CLINICAL MICROBIOLOGY REVIEWS, Apr. 2007, p. 323–367 Vol. 20, No. 2
0893-8512/07/$08.00+0 doi:10.1128/CMR.00031-06

Epidemiology and Control of Neosporosis and *Neospora caninum*

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INTRODUCTION

Neospora caninum is a protozoan parasite of animals. Until 1988, it was misdiagnosed as *Toxoplasma gondii* (138). Since its first recognition in 1984 in dogs in Norway (52) and the description of the new genus and species *Neospora caninum* by Dubey et al. (138), neosporosis has emerged as a serious disease of cattle and dogs worldwide. Abortions and neonatal mortality are a major problem in livestock operations, and neosporosis is a major cause of abortion in cattle. We have previously reviewed the general biology of *N. caninum* (130) and the pathogenesis and diagnosis of neosporosis in cattle (128, 133, 135, 158, 328). Although antibodies to *N. caninum* have been reported (275, 440), the parasite has not been demonstrated in human tissues. Thus, the zoonotic potential is uncertain. This review is focused on the epidemiology and control of neosporosis in cattle.

LIFE CYCLE

N. caninum is a coccidian parasite with a wide host range. In general, it is very similar in structure and life cycle to *T. gondii*, with two important differences: (i) neosporosis is primarily a disease of cattle, and dogs and related canids are definitive hosts of *N. caninum*, whereas (ii) toxoplasmosis is primarily a disease of humans, sheep, and goats, and felids are the only definitive hosts of *T. gondii*.

The life cycle is typified by the three known infectious stages: tachyzoites, tissue cysts, and oocysts (Fig. 1 and 2). Tachyzoites and tissue cysts are the stages found in intermediate hosts, and they occur intracellularly (152). Tachyzoites are approximately 6 by 2 μm (Fig. 2). Tissue cysts are often round or oval in shape, up to 107 μm long, and are found primarily in the central nervous system. The tissue cyst wall is up to 4 μm thick, and the enclosed bradyzoites are 7 to 8 by 2 μm. Extraneural tissues, especially muscles, may contain tissue cysts (155, 348).

The environmentally resistant stage of the parasite, the oocyst, is excreted in the feces of dogs and coyotes in an unsporulated stage (188, 270, 294). Oocysts sporulate outside the host in as few as 24 h (270). Nothing is known about the survival of *N. caninum* oocysts in the environment. Because of its close relationship with *T. gondii*, it is assumed that the environmental resistance of *N. caninum* oocysts is similar to that of *T. gondii* oocysts (131).

All three infectious stages of *N. caninum* (tachyzoites, bradyzoites, and oocysts) are involved in the transmission of the parasite. Carnivores probably become infected by ingesting tissues containing bradyzoites, and herbivores probably be-

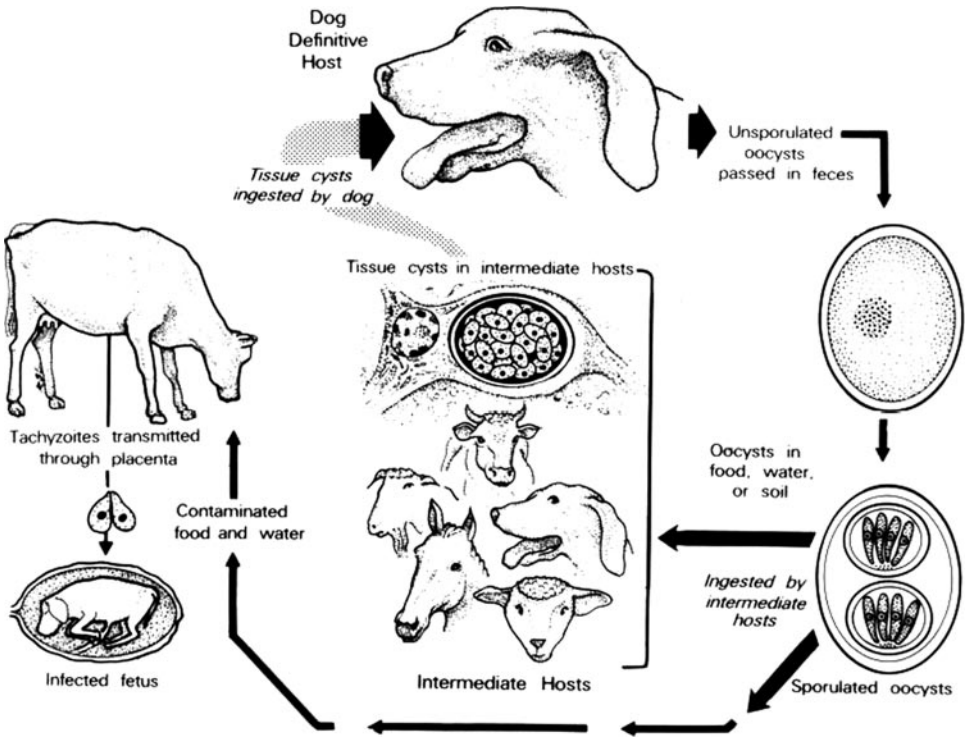

FIG. 1. Life cycle of *Neospora caninum*. (Reprinted from reference 128.)

come infected by the ingestion of food or drinking water contaminated by *N. caninum* sporulated oocysts. Transplacental infection can occur when tachyzoites are transmitted from an infected dam to her fetus during pregnancy.

HOST RANGE AND GEOGRAPHIC DISTRIBUTION

In order to understand the epidemiology of *N. caninum*, it is important to identify its host range and geographic distribution. Unlike *T. gondii*, viable *N. caninum* is difficult to isolate. Additionally, another species, *Neospora hughesi*, has been described as being isolated from horses (292). Therefore, we have made an attempt to identify different hosts of *N. caninum.*

Hosts Proven by Isolation of Viable *N. caninum* by Bioassays with Animals, Cell Culture, or Both

Viable *N. caninum* has been isolated from cattle, sheep, dogs, white-tailed deer, and water buffaloes (Table 1). Most of these isolates were from clinically affected animals and from neonatally infected animals, except for the isolates from buffaloes, sheep, and deer, which were from adult asymptomatic animals. Isolation of viable *N. caninum* has been achieved with a variety of cell cultures and by bioassays of immunosuppressed mice, gerbils, and dogs (135). Isolation in cell culture is limited by the necessity of having materials not contaminated with other microbes, and not all isolates can be adapted to grow in cell culture (457). Bioassays of immunosuppressed mice are expensive because outbred mice are not useful for propagating *N. caninum.* Isolation of *N. caninum* by feeding infected tissues to dogs and then examining canine feces for oocysts has the advantage that larger volumes of material can be fed to dogs than can ever be tested with cell culture or rodents. However, the identification of *N. caninum* in the feces of dogs should be based on the recovery of viable tachyzoites in cell culture or rodents inoculated with oocysts because of the existence of other *N. caninum*-like parasites in canine feces (403).

Hosts with *N. caninum*-like Parasites Demonstrated by Immunohistochemical (IHC) Staining of Parasites by Specific Antibodies, by *N. caninum* DNA, or by Both but Not by Isolation of Viable Parasites

N. caninum was demonstrated histologically in a few clinically affected deer, a raccoon, a rhinoceros, and goats, and DNA was found in a few animals (Table 2). We stress that finding DNA is not synonymous with finding viable *N. caninum*. Attempts to isolate viable *N. caninum* from rodent tissues that had demonstrable DNA were unsuccessful (235).

Serologic Prevalence of *N. caninum* Antibodies in Animals and Humans

Worldwide seroprevalences of *N. caninum* in dogs (Table 3), dairy cattle (Table 4), beef cattle (Table 5), other domestic animals (Table 6), wildlife and zoo animals (Table 7), and humans (Table 8) are summarized. Although these results are not comparable because of different serologic methods and different cutoff values used, they do provide evidence that many species of mammals have been exposed to this parasite. Many data summarized in Tables 3 to 8 are based on convenience samples obtained for other purposes. Also, the clinical status of the subjects surveyed was not stated, and in many of the reports, the prevalence of *N. caninum* was consistently higher in rural than

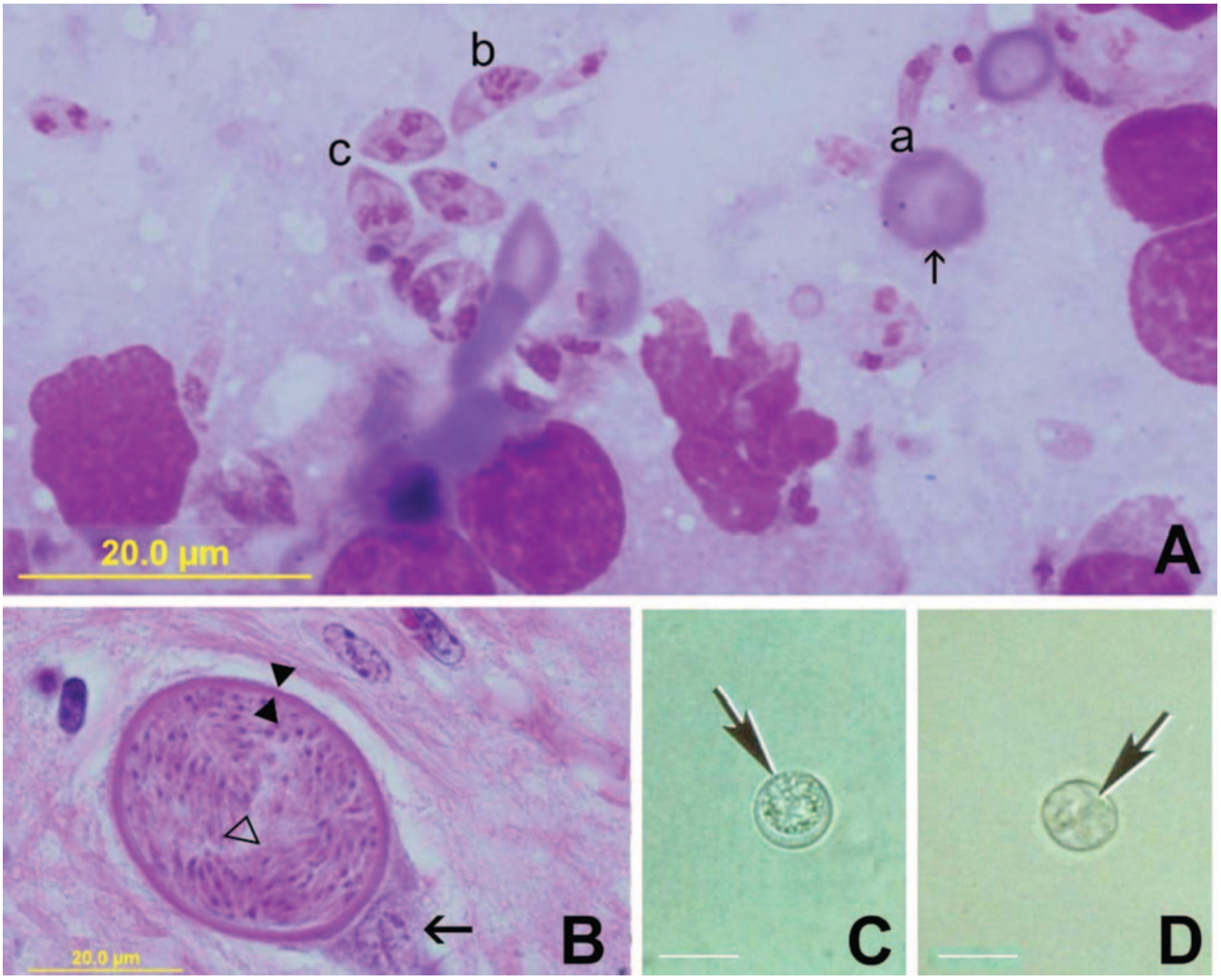

FIG. 2. Life cycle stages of *Neospora caninum*. (A) Impression smear of the liver of an experimentally infected mouse depicting numerous tachyzoites (Giemsa stain). Notice that the tachyzoites vary in dimension, depending on the stage of division: (a) a slender tachyzoite, (b) a tachyzoite before division, and (c) three dividing tachyzoites compared with the size of a red blood cell (arrow). (B) Histological section of a tissue cyst inside a neuron in the spinal cord of a congenitally infected calf (hematoxylin and eosin stain). Note the thick cyst wall (opposing arrowheads) enclosing slender bradyzoites (open triangle). The host cell nucleus (arrow) is cut at an angle. (C) Unsporulated oocyst (arrow) with a central undivided mass in the feces of a dog (unstained). Bar, 10 μm. (D) Sporulated oocyst (arrow) with two internal sporocysts (unstained). Bar, 10 μm.

in city dogs or pets (Table 3). In a well designed study, seroprevalences were compared in dairy and beef cattle from Germany, The Netherlands, Spain, and Sweden by use of randomized samples and enzyme-linked immunosorbent assays (ELISAs) that had been previously standardized among laboratories (39, 460). In this study, the seroprevalence in cattle in Sweden was much lower than in neighboring countries and prevalences in beef cattle were lower than in dairy cattle (Tables 4 and 5). As yet, there is no evidence that avian species are natural hosts for *N. caninum* (183).

None of the serologic tests used to detect *N. caninum* antibodies have been validated based on recovery of the viable parasite in any host. Therefore, the cutoff values used for serologic diagnosis of *N. caninum* are presumptive. Because *N. caninum* is structurally and molecularly related to *T. gondii*, these parasites are antigenically different and serologic cross-reactivity, if present, is considered minor. It is noteworthy that about 80% of black bears in the United States were found to be infected with *T. gondii*, but none had antibodies to *N. caninum* (136, 156).

Zoonotic Aspects of *N. caninum*

Because two rhesus monkeys (*Macaca mulatta*) have been successfully infected with *N. caninum* (35), there is concern about the zoonotic potential of *N. caninum*. However, at present there is no firm evidence that *N. caninum* successfully infects humans, because only low levels of antibodies have been reported (Table 8), and neither *N. caninum* DNA nor the parasite has been demonstrated in human tissues. As yet, no accidental *N. caninum* infections in persons handling viable organisms have been reported, and thus there are no reference sera with which to compare the results reported in Table 8.

TABLE 1. Intermediate and definitive host ranges and distributions of *N. caninum* or *N. hughesi* proven by isolation of the parasite

Host	Location	Tissue/origin	No. of isolates[a]	Reference(s)
Intermediate hosts				
Cow (*Bos taurus*)	Australia	Brain and spinal cord of a neonatal calf	1	305
	Brazil	Brains of a fetus and a 3-month-old calf	2	278, 279
	Italy	Brain of a 45-day-old calf	1	287, 288
	Japan	Brains and spinal cords of neonatal calves	5	490, 491
	Korea	Brains of a fetus and a neonatal calf	2	241, 242
	Malaysia	Brain of a neonatal calf	1	79
	New Zealand	Brains of neonatal calves	2	322
	Portugal	Brain of a fetus	1	67
	Spain	Brain of a fetus	1	68
	Sweden	Brain of a neonatal calf	1	421
	United Kingdom	Brains of a fetus and a neonatal calf	2	108, 441
	United States	Brains of fetuses and neonatal calves	8	86, 187, 291, 294, 296, 297
	The Netherlands	Placenta	3*	120
	Italy	Brain of an 8-month-old calf	1	172
	Japan	Brain of an adult cow	1	390
	New Zealand	Brain of an adult cow	1	322
Sheep (*Ovis ovis*)	Brazil	4-month-old sheep	1	342a
	Japan	Adult ewe	1	253
Water buffalo (*Bubalus bubalis*)	Brazil	Adult buffalo	5	373
Horse (*Equus caballus*)	United States	Neural tissue of adult horse	3†	78, 150, 292
White-tailed deer (*Odocoileus virginianus*)	Virginia	Brain of adult deer	3	457
	Illinois	Brain of adult deer	1‡	189
Dog (*Canis familiaris*)	Germany	Congenitally infected pup; neural tissue	1	347
	United Kingdom	Congenitally infected pup; neural tissue	1	28
	United States	Congenitally infected pups; neural tissue	10	101, 139, 144, 155, 208, 292
	Australia	Adult dog; skin	1	300
	Brazil	Adult dog; brain	1	186
Definitive host				
Dog (*Canis familiaris*)	Argentina	Feces	1§	44
	Germany	Feces	5§	403

[a] Symbols: *, oocyst isolates (see Table 9); †, *Neospora hughesi*; ‡, oocysts obtained in feces of dogs fed brains of infected deer but viable parasite not obtained in cell culture or mice; §, oocysts seen.

OOCYST SHEDDING BY DOGS AND OTHER DEFINITIVE HOSTS

Oocysts are the key in the epidemiology of neosporosis, but little is known of the biology of *N. caninum* oocysts. Dogs shed oocysts 5 days or more after ingesting tissues of experimentally or naturally infected animals (Table 9). The total duration of oocyst shedding after primary infection varied from 1 to several days. The total number of oocysts shed, prepatent periods, and duration of oocyst shedding varied tremendously (Table 9). Factors affecting oocyst shedding are largely unknown and difficult to investigate because of the costs involved in housing dogs in a secure facility and the low numbers of oocysts shed and because oocyst shedding is erratic (Table 9). Apparently dogs shed more oocysts after ingesting bovine tissues than when fed murine tissues (187), and pups shed more oocysts than adult dogs (Table 9). Some of the dogs that had been given corticosteroids shed more than 100,000 oocysts after being fed with murine brains, suggesting that immunosuppressed dogs may shed more oocysts than immunocompetent dogs (270, 273). Schares et al. (403) found the highest number of oocysts from a naturally infected dog. This dog was splenectomized. Nothing is known about the effect of differ-

TABLE 2. Host range and distribution of *N. caninum* demonstrated by IHC or DNA but not by isolation in noncanine, nonbovine domestic animals

Host	Location	Remarks	Reference
Red fox (*Vulpes vulpes*)	Catalonia, Spain	DNA detected in 10.7% of 122 fox brains	6
	Czech Republic	DNA detected in 4.6% of 152 fox brains	226
Raccoon (*Procyon lotor*)	United States	DNA- and IHC-positive brain of 1 raccoon	262
Antelope (*Tragelaphus imberbis*)	Germany	Three full-term dead calves; fetal antibody and lesions in all 3, DNA in tissues of 1; IHC negative	349
Black-tailed deer (*Odocoileus hemionus columbianus*)	United States	Tachyzoites found in lung and kidney of a 2-mo-old fawn; IHC-positive tachyzoites	482
Eld's deer (*Cervus eldi siamensis*)	France Zoological Park, Paris	IHC-positive parasites in the brain of a stillborn	142
Fallow deer (*Dama dama*)	Switzerland captive group	IHC-positive and PCR-positive parasites in central nervous system of a 3-wk-old calf	417
Llama (*Lama glama*)	Peru	IHC- and PCR-positive brain in 1 of 9 fetuses	409
Alpaca (*Vicugna pacos*)	Peru	IHC- and PCR-positive brain in 2 of 6 fetuses	409
Rat (*Rattus norvegicus*)	United Kingdom	DNA detected in 4.4% of 45 rats from sheep farms	223
	Taiwan	DNA detected in brains of 2 of 55 seropositive rats; parasite detected by bioassay in mice	222
	Grenada, West Indies	DNA detected in brains of 30% of 238 rats	235
Mouse (*Mus musculus*)	United Kingdom	DNA detected in brains of 3% of 100 mice from sheep farms	223
	United States	DNA detected in brains of 10% of 105 mice from Maryland	235
Rhinoceros (*Ceratotherium simum*)	South Africa	Tachyzoites found in sections of a 16-day-old calf that died suddenly; IHC positive	479
Goat (*Capra hircus*)	Rio Grande do Sul, Brazil	IHC-positive brain of a 3-day-old dairy goat	91
	Costa Rica	IHC-positive aborted dairy goat fetus	143
	Perugia, Italy	Histology positive, PCR positive	161
	California	IHC-positive brain from 2 aborted pygmy goat fetuses	34
	Pennsylvania	IHC-positive brain from 1 stillborn pygmy goat	141

ent breeds of dogs on oocyst shedding. In most experiments, hounds were used to collect oocysts (Table 9).

Oocyst Shedding by Naturally Infected Dogs

N. caninum-like oocysts have been identified in only a few dogs worldwide. Because *N. caninum* oocysts structurally resemble another coccidian in dog feces, *Hammondia heydorni* (403, 416, 419), it is epidemiologically important to properly identify *N. caninum* oocysts. Available information on oocyst shedding by naturally infected dogs is reviewed. To our knowledge, there are only a few reports of *N. caninum* oocyst shedding by naturally infected dogs (44, 299, 300, 403, 416). Basso et al. (44) found a few *N. caninum* oocysts in the feces of a 45-day old Rottweiler from La Plata, Argentina. Viable *N. caninum* was recovered from the gerbils that were fed these oocysts, and the strain was successfully cultured in vitro.

Šlapeta et al. (416) found 1 million oocysts in a 1-year-old German shepherd from the Czech Republic. The oocysts were considered *N. caninum* based on PCR, and bioassay was not reported.

McGarry et al. (299) examined a total of 15 fecal samples from two foxhound kennels in the United Kingdom (10 from one kennel of 80 and 5 from the second kennel of 60 dogs) and found *N. caninum* oocysts in two samples. One of these samples (from the pack of 60 foxhounds) was identified as *N. caninum* based on PCR; there were approximately 84 oocysts per gram of feces. A second fecal sample from this dog taken 4 months later revealed a few oocysts that were identified as *N. caninum* based on PCR.

McInnes et al. (300) detected *N. caninum* DNA in the feces of a dog in New Zealand 2.5 years after they had isolated viable *N. caninum* from the skin of the dog.

A comprehensive survey of *N. caninum* infection in the feces of dogs from Germany was reported by Schares et al. (403). *N. caninum*-like oocysts were found in 47 of 24,089 fecal samples. Twenty-eight of these fecal samples were bioassayed in gerbils. Based on seroconversion in bioassayed gerbils, seven samples were considered to be *N. caninum*. Five samples were definitively identified as *N. caninum*, based on successful in vitro cultivation. Among the other isolates, 12 were considered to be *H. heydorni*, 2 *T. gondii*, and 2 *Hammondia hammondi*. *T. gondii* and *H. hammondi* are pseudoparasites in dog feces and result from the ingestion of cat feces by dogs. This investigation highlights the difficulties of identification of *N. caninum* oocysts in canine feces.

TABLE 3. Prevalence of *N. caninum* antibodies in dogs

Country	Region	Type	No. tested	% Positive	Test[a]	Titer[b]	Reference
Argentina	Province of Buenos Aires	Urban	160	26.2	IFAT	1:50	45
		Dairy farm	125	48.0	IFAT	1:50	45
		Beef farm	35	54.2	IFAT	1:50	45
	La Plata	Pet	97	47.4	IFAT	1:50	127
Australia	Melbourne		207	5	IFAT	1:50	29
	Sydney		150	12	IFAT	1:50	29
	Perth		94	14	IFAT	1:50	29
Austria		Rural	433	5.3	IFAT	1:50	470
		Urban	381	2.1	IFAT	1:50	470
		Unknown	956	3.3	IFAT	1:50	470
Belgium		Dairy	56	46.4	ELISA	VMRD	259
				26.8	IFAT	1:100	259
		Clinic	84	18.4	ELISA	VMRD	259
		Asymptomatic		9.7	IFAT	1:100	259
		Sick	71	22.2	ELISA	VMRD	259
				11.3	IFAT	1:100	259
	Antwerp	Random	100	11	IFAT	1:50	30
	Ghent	Clinic	100	11	IFAT	1:50	30
	Ghent	Random	100	12	IFAT	1:50	30
Brazil	Bahia	Pet and street	415	12	IFAT	1:50	236a
	Mato Grosso do Sul	Urban	345	27.2	IFAT	1:50	15
	Mato Grosso do Sul	Pet	245	26.5	IFAT	1:50	117
	Mato Grosso do Sul	Rural	40	30	IFAT	1:100	14
	Maranhão	Street	100	45	IFAT	1:50	427
	Minas Gerais	Urban	300	10.7	IFAT	1:50	164
	Minas Gerais	Periurban	58	18.9	IFAT	1:50	164
	Minas Gerais	Rural	92	21.7	IFAT	1:50	164
	Minas Gerais	Clinical	163	6.7	IFAT	1:50	307
	Minas Gerais	Clinic	275	7.9	ELISA	WT-IH	308
	Minas Gerais	Stray	94	12.8	ELISA	WT-IH	308
	Minas Gerais	Clinic, stray	300	10.7	IFAT	1:25	414
	Paraíba	Domestic	286	8.4	IFAT	1:50	23
	Paraná	Dairy farm	134	21.6	IFAT	1:50	119
	Paraná	Urban, neurological	31	0	IFAT	1:50	184
	Paraná	Sheep farms	24	29.1	IFAT	1:50	374a
	Rondônia	Street	157	8.3	IFAT	1:25	71
	Rondônia	Street	174	12.6	IFAT	1:50	2
	São Paulo	Beef farm	39	58.9	IFAT	1:50	203
	São Paulo	Pet	500	10.0	NAT	1:25	181
	São Paulo	Street	611	25.0	NAT	1:25	181
	São Paulo	Rural and urban	295	8.4	IFAT	1:50	452
	São Paulo	Urban	204	17.6	IFAT	1:50	182a
Chile	IX Region	Rural	81	25.9	IFAT	1:50	341
		Urban	120	12.5	IFAT	1:50	341
		Dairy farm	7	57	IFAT	1:50	341
Czech Republic			80	1.3	ELISA	IH-ISCOM	252
			858	4.9	IFAT	1:50	448
Denmark		Pet	98	15.3	IFAT	1:160	362
Germany		Clinic	200	13	IFAT	1:50	246
		Normal	50	4	IFAT	1:50	246
Falkland Islands			500	0.2	IFAT	1:50	29
France		Dairy farm	22	22.7	IFAT	1:100	354
Hungary		Rural	249	6.0	IFAT	1:80	220
		Urban	402	1.0	IFAT	1:80	220
Iran		Rural	50	20.0	IFAT	1:50	290
		Urban	50	46.0	IFAT	1:50	290

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TABLE 3—*Continued*

Country	Region	Type	No. tested	% Positive	Test[a]	Titer[b]	Reference
Italy	Campania	Pet	1,058	6.4	IFAT	50	100
	Campania Parma	Pet	194	28.9	IFAT	1:50	99
		Pet	282	18.1	IFAT	1:50	254
	Veneto	Kennel and pet	707	10.9	ELISA	VMRD	73
	Southern Italy	Kennel	144	14.6	ELISA	MASTAZYME	334a
		Farm	162	26.5	ELISA	MASTAZYME	334a
Japan		Urban	198	7.1	IFAT	1:50	389
		Dairy farm	48	31.3	IFAT	1:50	389
Kenya		Rural	140	0	IFAT	1:50	29
Korea		Urban	289	8.3	IFAT	1:50	245
		Dairy farm	51	21.6	IFAT	1:50	245
Mexico	Hidalgo	Farm	27	51	ELISA	IDEXX	385
	Hidalgo	City	30	20	ELISA	IDEXX	385
The Netherlands		City	344	5.5	ELISA	WT-IH	489
		Farm	152	23.6	ELISA	WT-IH	489
New Zealand		Urban	150	76.0	IFAT	1:50	19
		Dairy farm	161	97.5	IFAT	1:50	19
		Beef/sheep farm	154	100	IFAT	1:50	19
		Farm	200	22	IFAT	1:40	366
Romania	Cluj Napoca	Stray	56	12.5	IFAT	ND	426
Spain	Catalonia	Pet	139	12.2	IFAT	1:50	330
Sweden		Pet	398	0.5	ELISA	IH-ISCOM	53
Switzerland		Pet	1,080	7.3	ELISA	WT-IH	384
		Dairy farm	30	20	ELISA	WT-IH	384
Taiwan		Dairy farm	13	23	IFAT	1:50	325
Tanzania		Rural	49	22	IFAT	1:50	29
Thailand		Dairy farm	82	1.2	ELISA	VMRD	256
Turkey	Bursa, Adana	Pet	150	10.0	IFAT	1:50	95
United Kingdom		Pet	104	5.8	IFAT	1:50	260
		Pet	163	16.6	IFAT	1:50	444
United States	Kansas	Pet	229	2	IFAT	1:50	265
	35 states	Pet	1,077	7	IFAT	1:50	76
Uruguay			414	20	IFAT	1:50	29

[a] NAT, *Neospora* agglutination test.
[b] WT, whole tachyzoite extract; IH, in house; IDEXX, IDEXX HerdChek *Neospora caninum* antibody (indirect ELISA, sonicate lysate of tachyzoites; IDEXX Laboratories, The Netherlands); VMRD, *Neospora caninum* cELISA (competitive ELISA, gp65 surface antigen of tachyzoites; VMRD); IH-ISCOM, detergent-extracted tachyzoite antigen incorporated into immune-stimulating complex particles; MASTAZYME, MASTAZYME NEOSPORA (indirect ELISA, formaldehyde-fixed whole tachyzoites; MAST GROUP, United Kingdom); ND, no data.

The number of *N. caninum* oocysts in naturally infected dog feces varied from a few to 114,000 per gram (in a 13-year-old dog that had been splenectomized). The infected dogs were 2 months to 13 years of age and were of seven different breeds (403).

Coyotes and Other Definitive Hosts of *N. caninum*

One of four captive-raised coyotes shed a few *N. caninum* oocysts after ingesting experimentally infected bovine tissues (188). *N. caninum* DNA was found in the feces of 2 of 85 coyotes and 2 of 271 foxes from Canada (471).

STRAIN VARIATION AND PATHOGENICITY

It is now well established that *N. caninum* can cause serious illness in cattle and dogs. Isolates of *N. caninum* from various hosts are genetically similar, although each strain has its own signature (365). Little is known of the strain variation with

TABLE 4. Serologic prevalence of *N. caninum* antibodies in dairy cattle

Country	Region	No. of animals (relevant details)	No. of herds	% Positive	Test[a]	Titer[b]	Reference(s)
Argentina	La Plata	33	3	51.5	IFAT	1:800	455
	La Plata	189 (abortion)	19	64.5	IFAT	1:25	456
		1,048	52	16.6	IFAT	1:200	310, 311
		750 (abortion)	49	43.1	IFAT	1:200	310, 311
Australia	New South Wales	266	1	24	IFAT	1:160	22
	New South Wales	266	1	10.2	ELISA	POURQUIER	200
Belgium		711	52	12.2	IFAT	1:200	112
Brazil	Bahia	447	14	14.0	IFAT	1:200	185
	Goiás	444	11	30.4	IFAT	1:250	304
	Minas Gerais	584	18	18.7	ELISA	IDEXX	114
	Minas Gerais	476	15	12.6	ELISA	IDEXX	115
	Minas Gerais	100	3	46.0	ELISA	IDEXX	115
	Minas Gerais	126		34.4	IFAT	1:25	361
	Minas Gerais	243	2	16.8	ELISA	IH-ISCOM	308a
	Mato Grosso do Sul	23		21.7	IFAT	1:25	361
	Paraná	165 (abortion)	1	42.1	ELISA	IDEXX	276
	Paraná	172	1	34.8	ELISA	IDEXX	277
	Paraná	623	23	14.3	IFAT	1:25	195
	Paraná	75		21.3	IFAT	1:25	361
	Paraná	385	90	12	IFAT	1:200	321a
	Rio Grande do Sul	223 (abortion)		11.2	IFAT	1:200	92
	Rio Grande do Sul	1,549	60	17.8	IFAT	1:200	93
	Rio Grande do Sul	70		18.6	IFAT	1:25	361
	Rio Grande do Sul	781 (dairy and beef)		11.4	ELISA	CHEKIT	459a
	Rio de Janeiro	75		22.7	IFAT	1:25	361
	Rio de Janeiro	563	57	23.2	ELISA	IDEXX	318
	Rondônia	1,011	50	11.2	IFAT	1:25	2
	São Paulo	150		27.3	IFAT	1:25	361
	São Paulo	521		15.9	IFAT	1:200	387
	São Paulo	521		30.5	ELISA	IDEXX	387
	São Paulo	408		35.5	ELISA	IDEXX	388[c]
Canada	Alberta	2,816	77	18.5	ELISA	IDEXX	406
	Manitoba	1,204	40	8.3	ELISA	IDEXX	451
	New Brunswick	900	30	25.5	ELISA	WT-IHCA	199, 240, 449
	Nova Scotia	900	30	21.3	ELISA	WT-IHCA	199, 240, 449
	Ontario	758	25	6.7	ELISA	WT-IHCA	159
	Ontario	3,412	56	7.0	ELISA	WT-IHCA	98
	Ontario	3,702	82	12.1	ELISA	WT-IHCA	217
	Ontario	3,162	57	10.5	ELISA	WT-IHCA	217
	Ontario	1,704	57	11.2	ELISA	WT-IHCA	217
	Ontario	9,723	125	11.2	ELISA	WT-IHCA	334
	Ontario, Prince Edward Island, New Brunswick, Nova Scotia	3,531	134	12.7	ELISA		439
	Ontario	930	31	8.2	ELISA	BIOVET	199
	Prince Edward Island	900	30	10.4	ELISA	WT-IHCA	199, 240, 449
	Québec	437	11	9.8	ELISA	BIOVET	25
	Québec	2,037	23	21.9	ELISA	BIOVET	47
	Québec	3,059	46	16.6	ELISA	WT-IHCA	339
	Saskatchewan	1,530	51	5.6	ELISA	BIOVET	450
Chile	IX Region	198	1	15.7	IFAT	1:200	340
		173	1	30.2	IFAT	1:200	340
Costa Rica		3,002	20	39.7	ELISA	WT-IHCA	376
		2,743	94	43.3	ELISA	WT-IHCA	378
Czech Republic		407 (abortion)	5	3.1	IFAT	1:200	447
		463 (abortion)	137	3.9	ELISA	IDEXX	447
Denmark		1,561	31	22	ELISA, IFAT	IH-ISCOM	236

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TABLE 4—*Continued*

Country	Region	No. of animals (relevant details)	No. of herds	% Positive	Test[a]	Titer[b]	Reference(s)
France	Normandy	575		26	ELISA	IDEXX	247
		1,924	42	5.6	ELISA	IDEXX	248, 333
		895		26	ELISA	IDEXX	353
		1,373	13	10.4	ELISA	IDEXX	353
		1,170	12	11.1	ELISA	IDEXX	354
		2,141		17	ELISA	IDEXX	354
Germany		388 (fecundity problems)	22	4.1	IFAT	1:400	89
		1,357					
		100		6.8	ELISA	IDEXX	473
		4,261	1	27	IFAT	1:50	391
			100	1.6	ELISA	IH-p38 (milk samples)	39
Hungary		97 (abortion)		10	ELISA	IH-ISCOM	219
		518	39	3.3	IFAT	1:100	221
Iran	Mashhad	810 (abortion)	4	15.1	IFAT	1:200	380
	Mashhad	337	30	46	ELISA	IDEXX	364
Ireland		324 (abortion)		12.6	IFAT	1:640	301
		165 (control)		3.0	IFAT	1:640	301
Italy		5,912 (abortion)		24.4	IFAT	1:640	287
	Parma	820 (abortion)		28.7	IFAT	1:160	165
		880 (abortion)	85	14	IFAT	1:160	165
	Potenza, Paduna	387		11.4	ELISA	CHEKIT	332
	Italian Apennines	864	81	30.8	ELISA	IDEXX	371
	Southern Italy	350	35	18.8	ELISA	MASTAZYME	334a
Japan		145 (abortion)		20	IFAT	1:200	250
	Nationwide	2,420		5.7	IFAT	1:200	250, 251
Korea	Nine provinces	793	168	20.7	IFAT	1:200	225
		895 (abortion)	30	48.7	IFAT	1:200	225
		492		23.0	ELISA	IgG-IH	24
		852		12.1	ELISA	IH-Ncp43P	3
Mexico	Aguascalientes	187 (abortion)	13	59	ELISA	IDEXX	179
	Coahuila, Chihuahua	813 (abortion)	20	42	ELISA	IDEXX	180
	Hidalgo, Queterado, Jalisco Coahuila Nuevo Leon	1,003	50	56	ELISA	WT-IH	315
	Tamaulipas	12	185	45	ELISA	WT-IH	302
		18	262	40	ELISA	WT-IH	302
		11	144	16	ELISA	WT-IH	302
The Netherlands		2,430	18	39.4	ELISA	WT-IH	121
		6,910	108	9.9	ELISA	WT-IH	39
New Zealand		77 (abortion)	1	46.7	IFAT	1:200	430
		97 (abortion)	1	30.7	IFAT	1:200	97
		800	40	7.6	ELISA	WT-IH	366
		194 (abortion)	1	53	ELISA	WT-IH	392
		600 (abortion)	1	50	ELISA	WT-IH	351
		1,199 (abortion)	3	33.6	IFAT	1:200	370
		164 (abortion)	1	10.9	IFAT	1:200	474
Paraguay		297	6	35.7	ELISA	WT-IH	331
People's Republic of China		262	9	17.2	ELISA	CIVTEST	492
Poland		45 (abortion)	6	15.6	ELISA	IDEXX	62
		416	32	9.3	ELISA	IDEXX	475

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TABLE 4—*Continued*

Country	Region	No. of animals (relevant details)	No. of herds	% Positive	Test[a]	Titer[b]	Reference(s)
Portugal		119 (abortion)	1	49	ELISA	IDEXX	429
		114	49	28	NAT	1:40	69
		1,237 (abortion)	36	46	NAT	1:40	69
Russia		391	8	9.9	ELISA		88
Slovakia		105 (abortion)		22.2	ELISA	IDEXX	158a
Spain		889	43	30.6	ELISA	WT-IHCA	289
		1,121	143	36.8	ELISA	WT-IH	359
		237 (abortion)	1	35.4	ELISA	IDEXX	281
		285 (breeder bulls)		11.2	IFAT	1:50	64
				11.2	ELISA	CIVTEST	64
				13.3	ELISA	IDEXX	64
		3,360	291	16.2	ELISA	CIVTEST	39
		2,773	6	15.1	ELISA	CIVTEST	282
		1,970 (abortion)	3	12	ELISA	CIVTEST	283
		1,331	2	26.8	ELISA	CIVTEST	284
Sweden		70 (abortion)	1	63	ELISA	IH-ISCOM	422
		>1,300	14	5.8–65	ELISA	IH-ISCOM	177
		4,252	112	1.3	ELISA	IH-ISCOM	39
		780		2	ELISA	IH-ISCOM	55
Taiwan		613	25	44.9	IFAT	1:200	325
Thailand	Eleven provinces	904		6	IFAT	1:200	425
		549	59	5.5	ELISA	VMRD	256
		83	16	37.5–70	IFAT	1:100	238
		164	11	15	ELISA	IH-ISCOM	74
Turkey	Ankara	60		10	ELISA	VRMD	255a
	Anatolia	3,287	32	13.9	ELISA	IDEXX	462
	Gebze	97		5.0	ELISA	VMRD	5
	Kars	228 (local)	14	0	ELISA	MASTAZYME	4
	Kars	73 (imported)	3	8.2	ELISA	MASTAZYME	4
	Thrace	274	6	8.0	ELISA	IDEXX	51
	Sakarya	92		9.2	ELISA	VMRD	324
	Sanliurfa	305		7.5	ELISA	VMRD	411
United Kingdom		95 (abortion)	1	60	ELISA	MASTAZYME	103
		4,295	14	17.1	ELISA	MASTAZYME	107
United States	California	176	1	34	IFAT	1:640	335
	California	277	1	43	IFAT	1:640	335
	California	285	2	40.4	ELISA	WT-IHCA	337
	California	254	1	60.6	ELISA	WT-IHCA	338
	Georgia	327	3	32.1	IB	Milk samples	326
	Maryland	1,029	1	28	IFAT	1:200	160
	Five regions	4,907	93 dairy, 5 beef	16	ELISA	IDEXX	374
	Oklahoma	1,000	16	14.7	ELISA	IDEXX	261
	Texas	87	2	10.3	IB	Milk samples	326
Uruguay		155	1	61.3	IFAT	1:200	239
Vietnam		200	>30	5.5	ELISA	IH-ISCOM	224

[a] NAT, *Neospora* agglutination test; IB, immunoblotting.

[b] WT, whole tachyzoite extract; IH, in house; WT-IHCA, kinetic ELISA (336); BIOVET, BIOVET-*Neospora caninum*, (indirect ELISA, sonicate lysate of tachyzoites; BIOVET Laboratories, Canada); CHEKIT, CHEKIT *Neospora* (indirect ELISA, detergent lysate of tachyzoites; IDEXX Laboratories, The Netherlands); IDEXX, IDEXX HerdChek *Neospora caninum* antibody (indirect ELISA, sonicate lysate of tachyzoites; IDEXX Laboratories); MASTAZYME, MASTAZYME NEOSPORA (indirect ELISA, formaldehyde-fixed whole tachyzoites; MAST GROUP, United Kingdom); VMRD, *Neospora caninum* cELISA (competitive ELISA, gp65 surface antigen of tachyzoites; VMRD); CIVTEST, CIVTEST BOVIS NEOSPORA (indirect ELISA, sonicate lysate of tachyzoites; Laboratorios Hipra S.A., Spain); IH-ISCOM, detergent-extracted tachyzoite antigen incorporated into immune-stimulating complex particles; IH-p38, native immunoaffinity-purified surface antigen NcSRS2; IH-Ncp43P, recombinant NcSRS2; NhSAG1, recombinant NhSAG1.

[c] Summary of other local surveys.

TABLE 5. Serologic prevalence of *N. caninum* antibodies in beef cattle

Country	Region	No. of animals (relevant details)	No. of herds	% Positive	Test[a]	Titer[b]	Reference(s)
Andorra		65	1	9.2	ELISA	CIVTEST	20
		1,758	26	7.4	ELISA	CIVTEST	20a
Argentina		400	17	4.7	IFAT	1:200	310, 311
		216 (abortion)	39	18.9	IFAT	1:200	310, 311
		305 (bulls)	19	4.9	IFAT	1:200	313
		290 (abortion)	1	20.3	IFAT	1:200	311, 312
Australia	Queensland	1,673	45	14.9	IFAT	1:200	424
Belgium		93		14	IFAT	1:200	113
Brazil	Goiás	456	9	29.6	IFAT	1:250	304
	Mato Grosso do Sul	241		26.1	ELISA	IDEXX	14
	Mato Grosso do Sul	87		29.9	IFAT	1:25	361
	Minas Gerais	36		11.1	IFAT	1:25	361
	Paraná	15		26.7	IFAT	1:25	361
	Rio de Janeiro	75		6.7	IFAT	1:25	361
	Rio Grande do Sul	70		21.4	IFAT	1:25	361
	Rondônia	584	11	9.5	IFAT	1:25	2
	São Paulo	505		20.0	ELISA	IDEXX	388[c]
	São Paulo	777	8	15.5	IFAT	1:200	202
	São Paulo and Minas Gerais	600		16.8	IFAT	1:200	96
Canada	Alberta	1,806	174	9.0	ELISA	IDEXX	468
	Alberta	1,976 (steers)	4 feed lots	6.5	ELISA	IDEXX	469
	Manitoba	1,425	49	9.1	ELISA	IDEXX	451
	Western Provinces	2,484	200	5.2	ELISA	BIOVET	463
Germany		2,022	106	4.1	ELISA	IH-p38	39
Hungary		545	49	1,8	IFAT	1:100	221
Italy	Potenza, Paduna	385	39	6.0	ELISA	CHEKIT	332
France		219		4.1	ELISA	ND	247
Japan		65		1.5	IFAT	1:200	250
Korea	Nine provinces	438		4.1	IFAT	1:200	243
Mexico	Linares	29	2	10	ELISA	WT-IH	302
	Pesqueria	30	1	10	ELISA	WT-IH	302
The Netherlands		1,601	82	13.3	ELISA	WT-IH	39
New Zealand		499	40	2.8	ELISA	WT-IH	428
Paraguay		582	5	26.6	ELISA	WT-IH	331
Spain		1,712	216	17.9	ELISA	WT-IH	359
	Galicia	2,407	372	15.8	ELISA	CIVTEST	39
United States	Western states	2,585	55	23	ELISA	VMRD	386
	Texas	1,009	92	12.9	NAT	1:80	31
	Nebraska	208 (abortion)	1	79	ELISA	IH-ISCOM	296
	North Dakota	212	7	5.2	ELISA	IDEXX	240a
Uruguay		4,444	229	13.9	ELISA	WT-IH	26

[a] NAT, *Neospora* agglutination test.

[b] WT, whole tachyzoite extract; IH, in house; BIOVET, BIOVET-*Neospora caninum*, (indirect ELISA, sonicate lysate of tachyzoites; BIOVET Laboratories, Canada); CHEKIT, CHEKIT *Neospora* (indirect ELISA, detergent lysate of tachyzoites; IDEXX Laboratories, The Netherlands); IDEXX, IDEXX HerdChek *Neospora caninum* antibody (indirect ELISA, sonicate lysate of tachyzoites; IDEXX Laboratories); VMRD, *Neospora caninum* cELISA (competitive ELISA, gp65 surface antigen of tachyzoites; VMRD); CIVTEST, CIVTEST BOVIS NEOSPORA (indirect ELISA, sonicate lysate of tachyzoites; Laboratorios Hipra S.A., Spain); IH-ISCOM, detergent-extracted tachyzoite antigen incorporated into immune-stimulating complex particles; IH-p38, native immunoaffinity-purified surface antigen NcSRS2.

[c] Summary of other local surveys.

TABLE 6. Prevalence of antibodies to *N. caninum* in noncanine, nonbovine domestic animals

Host	Location[a]	No. examined (relevant details)	% Positive[b]	Test[c]	Titer[d]	Reference
Domestic cat (*Felis domesticus*)	Brazil	502	11.9	NAT	1:40	151
	Brazil	400	24.5	IFAT	1:16	60
	Italy	282	31.9	NAT	1:40	169
Camel (*Camelus dromedarius*)	Egypt	161	3.7	NAT	1:40	214
	Iran	120	5.8	IFAT	1:20	381
Pig (*Sus scrofa*)	Germany	2,041 (from 94 farms)	3.3	ELISA	WT-IH	102
			0.04	ELISA/IB*		102
	United Kingdom	454	0	IFAT	1:50	209
Sheep (*Ovis ovis*)	Rio Grande do Sul, Brazil	62	3.2	ELISA	CHEKIT	459a
	Paraná, Brazil	305	9.5	IFAT	1:50	374a
	São Paulo, Brazil	597	9.2	IFAT	1:50	170
	Switzerland*	117	10.3	IFAT	1:160	207
	United Kingdom	660 (abortion)	0.45	IFAT	1:50	209
	Italy	1,010	2	ELISA	CHEKIT	178a
Goat (*Capra hircus*)	Costa Rica	81	6.1	IFAT	1:100	143
	Sri Lanka	486	0.7	ELISA†	WT-IH	320
	São Paulo, Brazil	394	6.4	IFAT	1:50	171
	Taiwan	24	0	IFAT	1:200	325
Llama (*Lama glama*)	Peru	81	1.2	IB		480
	Peru	73	32.9	IFAT	1:50	75
	Germany	20	0	IB		480
Alpaca (*Vicugna pacos*)	Peru	657	2.6	IB		480
	Peru	78	35.9	IFAT	1:50	75
	Germany	12	0	IB		480
	Minnesota	61	13.1	IFAT	1:50	189
Vicugna (*Vicugna vicugna*)	Peru	114	0	IB		480
Water buffalo (*Bubalus bubalis*)	São Paulo, Brazil	222	53	NAT	1:40	178
	Pará, Brazil	196	70.9	IFAT	1:25	182
	São Paulo, Brazil	411	56	IFAT	1:200	118
	Rio Grande do Sul, Brazil	164	14.6	ELISA	CHEKIT	459a
	Egypt	75	60	NAT	1:40	145
	Campana, Italy	1,377	34.6	IFAT	1:200	194
	People's Republic of China	40	0	ELISA	CIVTEST	492
	Vietnam	200	1.5	IFAT	1:640	224
Horse (*Equus caballus*)	Argentina	76	0	NAT	1:40	148
	Several regions, Brazil	101	0	NAT	1:40	149
	Several regions, Brazil	961	2.5	ELISA	NhSAG1	216
	Paraná, Brazil	36	47	IFAT	1:50	280
	São Paulo, Brazil	1106	10.3	IFAT	1:50	458
	VIII, IX Regions, Chile	145	32	NAT	1:40	342
	France	434	23	NAT	1:40	355
	France	50	6	NAT	1:100	357
	France	54 (abortion)	50	NAT	1:40	356
	France	45 (random)	77.7	NAT	1:40	356
	France	76 (random)	77.6	NAT	1:40	356
	Caserta, Napoli, Salerno, Italy	150	28	IFAT	1:50	81
	Jeju Island, South Korea	191	2	IFAT	1:50	196

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TABLE 6—*Continued*

Host	Location[a]	No. examined (relevant details)	% Positive[b]	Test[c]	Titer[d]	Reference
	Sweden	414	9	ELISA	IH-ISCOM	231
	Sweden		1*	IB		231
	Alabama	536	11.5	IFAT	1:50	78
	Texas, Nebraska	296	21.3	NAT	1:40	147
	Five geographic areas, United States	208	17	IFAT	1:100	454
	Washington	160 (normal)	8	IFAT	1:50	298
	Washington	140 (abortion)	13	IFAT	1:50	298
	Wyoming	276	31.1	NAT	1:25	153
	Many states, United States	1,917	30.4	ELISA	NhSAG1	215

[a] *, flock with endemic abortion.
[b] *, ELISA-positive samples ($n = 39$) were tested by immunoblotting.
[c] NAT, *Neospora* agglutination test; IB, immunoblotting. *, ELISA results confirmed by immunoblotting; †, confirmed by IFAT.
[d] WT, whole tachyzoite extract; IH, in house; CIVTEST, CIVTEST BOVIS NEOSPORA (indirect ELISA, sonicate lysate of tachyzoites; Laboratorios Hipra S.A., Spain); IH-ISCOM, detergent-extracted tachyzoite antigen incorporated into immune-stimulating complex particles; NhSAG1, recombinant NhSAG1.

respect to pathogenicity. There are no suitable animal models for testing strain variation. In limited studies, some *N. caninum* strains were more pathogenic to mice than others (21, 264, 268, 300). Abortion or fetal infections have been induced in cattle by using a variety of isolates in different laboratories (158), but a meaningful comparison with pregnant cattle would be economically prohibitive. There is the additional complication of the stage of the parasite used and the source of the parasite. Most *N. caninum* strains are maintained in cell culture, and prolonged passage in culture can alter the pathogenicity and other characteristics of the parasite (42, 346). Additionally, data obtained from rodents may not be applicable to cattle.

TRANSMISSION

Transmission in All Hosts

N. caninum can be transmitted postnatally (horizontally, laterally) by ingestion of tissues infected with tachyzoites or tissue cysts or by ingestion of food or drinking water contaminated by sporulated oocysts, or it can be transmitted transplacentally (vertically, congenitally) from an infected dam to her fetus during pregnancy. Recently, the terms "exogenous transplacental transmission" and "endogenous transplacental transmission" have been proposed to describe more precisely the origin of the transplacental infection of the fetus (442). Exogenous transplacental transmission occurs after a primary, oocyst-derived, infection of a pregnant dam, while endogenous transplacental transmission occurs in a persistently infected dam after reactivation (recrudescence) of the infection during pregnancy. Mice were infected successfully by oral inoculation of tachyzoites or bradyzoites (264). These results are of interest because tachyzoites treated with acidic pepsin were rendered noninfective for cell cultures, whereas bradyzoites survived the acidic pepsin (264). Tissue cysts and bradyzoites can survive up to 2 weeks at refrigeration temperature (4°C) but are killed by freezing (155, 267). Oocysts were orally infective to cattle (111, 190, 443), goats and sheep (397), and rodents such as mice, gerbils (*Meriones unguiculatus*), and guinea pigs (*Cavia porcellanus*) (134, 294, 397). Transplacental transmission has been induced experimentally in cattle, dogs, sheep, goats, monkeys, cats, and mice and occurs naturally in many hosts (133). Transplacental transmission occurs when tachyzoites from the dam cross the placenta. The ingestion of oocysts is the only demonstrated mode for postnatal (horizontal) transmission in herbivores. Because of the epidemiological importance, we will discuss the modes of transmission of *N. caninum* in dogs and cattle separately.

Transmission of *N. caninum* in Dogs

How dogs become infected with *N. caninum* in nature is not fully understood. Historically, vertical transmission of neosporosis was first recognized in dogs (52, 140). Three successive litters from a bitch in Norway were found to have neosporosis (52). In a retrospective study, the most severe neosporosis was discovered in four German Shepherds from one owner in 1957 from Ohio (140), and there was evidence that a congenitally infected bitch transmitted the infection to her progeny (140). Transplacental transmission in experimentally infected dogs has been demonstrated (82, 132). In most cases of neonatal neosporosis, clinical signs are not apparent until 5 to 7 weeks after birth (133). These data suggest that *N. caninum* is transmitted from the dam to the neonates toward the terminal stages of gestation or postnatally via milk. According to Barber and Trees (27), vertical transmission of *N. caninum* in dogs is considered highly variable and not likely to persist in the absence of horizontal infection. In a prospective study, only 3% (4 of 118) of pups from 17 seropositive bitches were seropositive. Overall, 80% of pups born to seropositive bitches were considered to be uninfected with *N. caninum* (133). These results are supported by a recent study in which 3 of 11 pups in the first litter and only 1 of 7 pups in the second litter were infected with *N. caninum* (157). These results obtained with dogs are dramatically different from those obtained with cattle.

Age-related prevalence data indicate that the majority of dogs become infected after birth. Higher prevalences have been documented in older than in younger dogs (15, 45, 73, 117, 119, 290, 334a, 489).

In one report, 51% of 300 foxhounds fed bovine carcasses were found to have *N. caninum* antibodies (441). While consumption of aborted bovine fetuses does not appear to be an important source of *N. caninum* infection in dogs (48, 123), the consumption of bovine fetal membranes may be a source of *N. caninum* for dogs. The parasite has been found in naturally infected placentas (49, 172, 412), and dogs fed placentas from freshly calved seropositive cows may shed *N. caninum* oocysts

TABLE 7. Seroprevalence of *Neospora caninum* antibodies in wildlife

Animal species	Country	Region/setting	No. examined	Test[a]	Titer[b]	% Positive	Reference
Canids							
Australian dingo (*Canis familiaris dingo*)	Australia	Queensland	52	IFAT	1:50	27	29
	Australia	New South Wales	117	IFAT	1:50	0.9	29
Coyote (*Canis latrans*)	Canada	Prince Edward Island	183	NAT	1:25	14.8	472
					1:100	0.5	472
	United States	Colorado	28	IFAT	1:50	17.9	189
	United States	Illinois	40	IFAT	1:50	15	189
	United States	Texas	52	IFAT	1:25	10	269
	United States	Utah	45	IFAT	1:50	2.2	189
Eurasian wolf (*Canis lupus dingo*)	Czech Republic	Zoo	10	IFAT	1:40	20	407
Wolf (*Canis lupus*)	Brazil	Zoo	59	IFAT	1:25	8.5	413
	Israel		9	IFAT	1:40	0	420
	United States	Alaska	122	NAT	1:40	3.2	136
	United States	Minnesota	164	IFAT	1:40	39	189
Golden jackal (*Canis aureus*)	Israel		114	IFAT	1:50	1.7	420
Maned wolf (*Chrysocyon brachyurus*)	Brazil	Zoo	59	IFAT	1:25	8.5	459
	Brazil	Zoo	48	IFAT	1:50	0	303
	Czech Republic	Zoo	6	IFAT	1:40	16.6	407
	Israel		9	IFAT	1:400	11.1	420
Red fox (*Vulpes vulpes*)	Austria		94	IFAT	1:50	0	470
	Belgium		123	IFAT	1:64	78	61
	Canada	Prince Edward Island	270	NAT	1:25	34.8	472
	Canada	Prince Edward Island	270	NAT	1:100	5.6	472
	Germany	Fur farm	122	IB		2.5	395
	Hungary		337	ELISA	IH-ISCOM	1.5	232
	Ireland		70	IFAT	1:20	1.4	481
	Israel		24	IFAT	1:50	4.1	420
	Sweden		221	ELISA	IH-ISCOM	0	230
	United Kingdom		546	IFAT	1:256	0.9	202
	United Kingdom		54	IFAT	1:50	2	29
	United Kingdom		16	IFAT	1:50	6	415
Gray fox (*Urocyon cinereoargenteus*)	United States	South Carolina	26	NAT	1:25	15.4	272
Chiloe fox (*Pseudalopex fulvipes*)	Chile	Zoo	2	NAT	1:320	100	341
Fennec (*Vulpes zerda*)	Czech Republic	Zoo	2	IFAT	1:320	100	407
Azara's fox (*Lycalopex gymnocercus*)	Brazil		12	IFAT, NAT	1:40–50	41.6	72
Crab-eating fox (*Cerdocyon thous*)	Brazil		15	IFAT	1:40–50	26.6	72
	Brazil		2	IFAT, NAT	1:40–50	0	72
Hoary fox (*Dusicyon vetulus*)	Brazil		30	IFAT	1:50	0	303
Raccoon dog (*Nyctereute procyonoides*)	Korea		26	NAT	1:50	23	245
Felids							
Cheetah (*Acinonyx jubatus*)	Czech Republic	Zoo	15	IFAT	1:40	13.3	407
	Kenya		5	NAT	1:40	60	168
	S. Africa		16	IFAT	1:50	6.3	77
Jaguarundi (*Herpailurus yaguarondi*)	Czech Republic	Zoo	1	IFAT	1:40	100	407
Eurasian lynx (*Lynx lynx*)	Czech Republic	Zoo	2	IFAT	1:40	50	407
Indian lion (*Panthera leo goojratensis*)	Czech Republic	Zoo	2	IFAT	1:40	50	407
Lion (*Panthera leo*)	S. Africa		18	IFAT	1:50	16.6	77
	Kenya		20	NAT	1:40	55	168
Other carnivores							
Hyena (Crocuta crocuta)	Kenya		3	NAT	1:40	33.3	168
Fisher (*Martes pennanti*)	Czech Republic	Zoo	2	IFAT	1:40	50	407
Raccoon (*Procyon lotor*)	United States	Massachusetts, Florida, Pennsylvania, New Jersey	99	NAT	1:50	10	271
Black bear (*Ursus americanus*)	United States	North Carolina	64	NAT	1:40	0	136
		Pennsylvania	133	NAT	1:40	0	136
Equids							
Zebra (*Equus burchelli*)	Kenya		41	NAT	1:40	70.7	168
Cervids and ruminants							
Blackbuck (*Antilope cervicapra*)	Czech Republic	Zoo	9	IFAT	1:40	22.2	407

Continued on following page

TABLE 7—*Continued*

Animal species	Country	Region/setting	No. examined	Test[a]	Titer[b]	% Positive	Reference
Lechwe (*Kobus leche*)	Czech Republic	Zoo	4	IFAT	1:40	25	407
African buffalo (*Syncerus caffer caffer*)	Czech Republic	Zoo	5	IFAT	1:40	20	407
	Kenya		4	NAT	1:40	50	168
Impala (*Aepyceros melampus*)	Kenya		14	NAT	1:40	14.3	168
Gazelle (*Gazella thomsoni*)	Kenya		26	NAT	1:40	26.9	168
Spanish ibex (*Capra pyrenaica hispanica*)	Spain		3	ELISA	POURQUIER	0	7
Mouflon (*Ovis ammon*)	Spain		27	ELISA	POURQUIER	0	7
Barbary sheep (*Ammotragus lervia*)	Spain		13	ELISA	POURQUIER	7.7	7
Eland (*Taurotragus oryx*)	Czech Republic	Zoo	12	IFAT	1:40	8.3	407
	Kenya		13	NAT	1:40	92.3	168
European bison (*Bison bonasus*)	Czech Republic	Zoo	4	IFAT	1:40	25	407
	Poland		320	ELISA	IDEXX	7.3	63
Bison (*Bison bison*)	United States	Alaska	219	NAT	1:40	0.4	136
		Iowa	30	NAT	1:40	13.3	136
Musk ox (*Ovibos moschatus*)	United States	Alaska	224	NAT	1:40	0.44	136
Sitatunga (*Tragelaphus spekei gratus*)	Czech Republic	Zoo	7	IFAT	1:40	14.3	407
Père David's deer (*Elaphurus davidianus*)	Czech Republic	Zoo	28	IFAT	1:40	25	407
Brocket deer (*Mazama* sp.)	Brazil		150	IFAT	1:50	42	438
Pampas deer (*Ozotoceros bezoarticus*)	Brazil	Goiás	23	IFAT	1:50	13	437
	Brazil	Mato Grosso	16	IFAT	1:50	75	437
Thorold's deer (*Cervus albirostris*)	Czech Republic	Zoo	7	IFAT	1:40	57.1	407
Red deer (*Cervus elaphus*)	Italy	Italian Alps	102	IFAT	1:40	12.7	167
	Italy	Trentino	125	c-ELISA	VMRD	3.2	59a
	Spain		237	ELISA	POURQUIER	11.8	7
Vietnam sika deer (*Cervus nippon pseudaxis*)	Czech Republic	Zoo	3	IFAT	1:160	33.3	407
Roe deer (*Capreolus capreolus*)	Italy	Italian Alps	43	IFAT	1:40	37.2	167
	Italy	Central Italian Alps	117	IFAT	1:50	3	178a
	Italy	Trentino	66	c-ELISA	VMRD	7.6	59a
	Spain		33	ELISA	POURQUIER	6.1	7
Fallow deer (*Dama dama*)	Spain		79	ELISA	POURQUIER	0	7
White-tailed deer (*Odocoileus virginianus*)	United States	Illinois	400	NAT	1:40	40.5	146
	United States	Illinois	43	IFAT	1:100	46.5	189
	United States	Minnesota	150	IFAT	1:100	20.0	189
	United States	Missouri	23	IB		48	13
	United States	Wisconsin	147	IB		20	13
	United States	14 southwestern states	305	NAT	1:25	48	274
Chamois (*Rupicapra pyrenaica*)	Spain		40	ELISA	POURQUIER	0	7
Chamois (*Rupicapra rupicapra*)	Italy	Italian Alps	119	IFAT	1:40	29.4	167
	Italy	Central Italian Alps	67	IFAT	1:50	21	178a
	Italy	Trentino	503	c-ELISA	VMRD	1.4	59a
Eastern elk (*Cervus elaphus canadensis*)	Czech Republic	Zoo	1	IFAT	1:1280	100	407
Caribou (*Rangifer tarandus*)	United States	Alaska	160	NAT	1:40	3.1	136
Moose (*Alces alces*)	United States	Alaska	162	NAT	1:40	2.4	136
	United States	Minnesota	61	IFAT	1:100	13.1	189
Rodents							
Wild rabbit (*Oryctolagus cuniculus*)	Spain		251	ELISA	POURQUIER	0	7
Hare (*Lepus granatensis*)	Spain		53	ELISA	POURQUIER	1.8	7
Hare (*Lepus europaeus*)	Hungary		93	NAT	1:40	8.6	163
	Slovakia		44	NAT	1:40	6.8	163
Rat (*Rattus norvegicus*)	Grenada		242	NAT	1:20	4.6	235
Mouse (*Mus musculus*)	United States		79	NAT	1:20	5.0	235
Marine mammals							
Sea otter (*Enhydra lutris*) (dead)	United States	California, Washington	115	NAT	1:40	14.8	154
Sea otter (live)	United States	Washington	30	NAT	1:40	36.7	154
Walrus (*Odobenus rosmarus*)	United States	Alaska	53	NAT	1:40	5.6	154
Sea lion (*Zalophus californianus*)	United States	Alaska	27	NAT	1:40	3.7	154
Harbor seal (*Phoca hispida*)	United States	Alaska	331	NAT	1:40	3.5	154
Ringed seal (*Phoca vitulina*)	United States	Alaska	32	NAT	1:40	12.5	154
Bearded seal (*Erignathus barbatus*)	United States	Alaska	8	NAT	1:40	12.5	154
Spotted seal (*Phoca largha*)	United States	Alaska	9	NAT	1:40	0	154
Ribbon seal (*Phoca fasciata*)	United States	Alaska	14	NAT	1:40	0	154

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TABLE 7—*Continued*

Animal species	Country	Region/setting	No. examined	Test[a]	Titer[b]	% Positive	Reference
Dolphin (*Tursiops truncatus*)	United States	Florida	47	NAT	1:40	91.4	154
Killer whale (*Orcinus orca*)	Japan		8	IB		12.5	323
Other land mammals							
Wild boar (*Sus scrofa*)	Spain		298	ELISA	POURQUIER	0.3	7
	Czech Republic		565	cELISA	VMRD	18.3	43
				IFAT	1:40	10.2	43
Warthog (*Phacochoerus aethiopicus*)	Kenya		6	NAT	1:40	66.7	168
Common brushtail opossum (*Trichosurus vulpecula*)	Australia		142	NAT	1:25	0	162

[a] IB, immunoblotting; NAT, *Neospora* agglutination test.
[b] WT, whole tachyzoite extract; IH, in house; IDEXX, IDEXX HerdChek *Neospora caninum* antibody (indirect ELISA, sonicate lysate of tachyzoites; IDEXX Laboratories); VMRD, *Neospora caninum* cELISA (competitive ELISA, gp65 surface antigen of tachyzoites; VMRD); CIVTEST, CIVTEST BOVIS NEOSPORA (indirect ELISA, sonicate lysate of tachyzoites; Laboratorios Hipra S.A., Spain); IH-ISCOM, detergent-extracted tachyzoite antigen incorporated into immune-stimulating complex particles.

(120). That dogs can become infected by ingesting infected tissues has been amply demonstrated (Table 9), but whether they can be infected by the ingestion of oocysts is unknown.

Transmission of *N. caninum* in Cattle

Transplacental (vertical) transmission. *N. caninum* is one of the most efficiently transplacentally transmitted parasites among all known microbes in cattle. In certain herds, virtually all calves are born infected but asymptomatic. Evidence for this efficient transplacental transmission comes from several sources: familial, comparison of antibody status in cows and their progeny, infection status of progeny, and experimental.

Björkman et al. (54) traced the familial history of *N. caninum*-seropositive dairy cows in a herd in Sweden and found that all infected animals were the progeny of two cows that were bought when the herd was established 16 years earlier. Insemination records suggested that venereal transmission was not a factor. Similar results were obtained in studies performed in Germany (391), Canada (47), Australia (201), and Sweden (176). A strong evidence for transplacental transmission of *N. caninum* has been obtained by comparison of seroprevalence in dams and their progeny. In cattle and other ruminants, there is no transfer of antibodies from the dam to the fetus, not even through a placenta that has been damaged by an infectious process (137). Therefore, detection of specific antibodies in precolostral serum indicates in utero synthesis of antibodies by the fetus. However, a finding of no antibody in the fetus is not conclusive of the absence of infection, because the fetus might have been infected late in gestation, leaving insufficient time for anti-

TABLE 8. Seroprevalence of *N. caninum* in humans

Country	Source of sample	No. of sera	Test	% Positive	Reference
Brazil	AIDS	61	IFAT (1:50)[a] ELISA IB	38	275
	Neurological disorders	50		18	
	Newborns	91		5	
	Controls	54		6	
Denmark	Repeated miscarriage	76	ELISA IFAT (1:640) (ISCOM) IB	0	350
Korea	Blood donors	172	IFAT (1:100) ELISA IB	6.7	321
Northern Ireland	Blood donors	247	IFAT (1:160)	8	193
United Kingdom	Farm workers and women with miscarriage	400	IFAT (1:400)	0	441
United States	Blood donors	1,029	IFAT (1:100) (1:200) IB[b]	6.7 0 +	440

[a] Sera were tested by IFAT at a 1:50 serum dilution and by ELISA (whole tachyzoites, in-house test); those with discrepant findings were tested by immunoblotting (IB).
[b] Sixteen of the samples that were positive by IFAT were positive by IB.

TABLE 9. Details of *N. caninum* oocyst shedding by dogs

Tissue fed[a]	No. of dogs		Days of oocyst shedding[b]	No. of oocysts isolated[c]	Observation period (no. of days)	Seroconversion (no. of dogs/ total)	Reference(s)
	Total fed	Shedding oocysts					
Experimentally infected							
Mouse brain; NC 2	3	2	8–27	ND	37	3/3	294
			13–23				
Mouse brain; NC-beef	2	1	13–20	ND	37	1/2	294
Mouse brain; NC-Liverpool	2	1	13–20	ND	37	2/2	294
Mouse brain; NC-beef	2	2	5, 6	4,500,000	42	1/2	270
				Few			
Mouse brain; wild CKO	3	1	13	Few	36	3/3	273
Mouse brain; cloned CKO	3	2	7–14	810,000	36	3/3	273
			8–13, 15	161,000	36	2/3	273
Mouse brain; NC 2	2	2	17, 19, 21, 22, 24	700	30	ND	187
			6–11, 13–17	29,900			
Mouse brain; NC-beef	2	2	9, 17, 21, 25	500	30	ND	187
			9, 10, 12–14	1,200			
Mouse brain; NC-IL	2	2	10, 13, 16, 17	300	30	ND	187
			6	100			
BALB/c mouse	1	0			ND	0/1	396, 397
Multimammate rat (all except skin); HY-Berlin-1996*	1	1	9–13	0	ND	ND	396, 397
Guinea pig (all except skin, stomach, and intestine); HY-Berlin-1996*	2	2	5–12	2,000,000	ND	1/2	396, 397
			5–11	1,000,000	ND		
Guinea pig (all except skin); HY-Berlin-1996*	1	1	5–14	0	ND	ND	396, 397
Guinea pig (skeletal muscle and bones); HY-Berlin-1996	2	2	8–13	Few	ND	0/2	396, 397
			11–13	Few	ND		
Infected sheep tissue (heart and skeletal muscle); HY-Berlin-1996*	8	7	9–13	1,500,000	ND	0/5	396, 397
			6–10	Few	ND		
			6–10	0	ND		
			7–11	Few	ND		
			7–13	Few	ND		
			8–13	0	ND		
			8–13	0	ND		
Infected goat tissue (heart and skeletal muscle); HY-Berlin-1996*	1	0		0	ND	ND	396, 397
Infected goat tissue (brain, heart, and skeletal muscle); HY-Berlin-1996*	3	3	7–12	0	ND	0/3	396, 397
			7–10	Few	ND		
			6–12	80,000	ND		
Calf; NC-beef	4	3	5–8, 11, 14–17	54,100	30	ND	187
			5–14, 16, 19	392,800			
			5–13, 20–21	503,300			
Calf; NC-IL	4	4	8–10, 13–16, 19, 20	25,100	30	ND	187
			7–9	5,700			
			10–13, 18–26, 29	345,900			
			6–10, 14–16	95,700			
Infected cattle tissue	5 (adults)	3	ND	2,000	28	4/5	191
				1,200			
				11,400			
Infected cattle tissue	3 (pups)	3	ND	504,400	28	2/3	191
				45,200			
				500			
Naturally infected							
Cattle placenta	3	3	13, 15, 16, 25, 27, 30	<10*	60	0/3	120
			11–16, 18	<10*			
			10–19, 21	<10*			
White-tailed deer brain	4	2	7–14	12,300†	ND	ND	189
			11, 12	500‡			
Water buffalo brain	7	4	26*	275,969	30	2/4	373
			17	820,655			
			7	21,265			
			9	43,500			

[a] *, *N. caninum* isolate originally named *Hammondia heydorni* Berlin-1996 (HY-Berlin-1996), because at the time of isolation the dog had not yet been established as a definitive host of *N. caninum*.
[b] Days of oocyst shedding after feeding of the infected meal. *, indicates a total of 26 days.
[c] ND, not determined; *, per gram of feces; †, PCR positive and infective to cattle; ‡, PCR and bioassay not done.

TABLE 10. Asymptomatic congenital transmission of *N. caninum* in cattle

Country	Region	No. of dams or pregnancies (relevant details)[a]	% Seropositivity in progeny	Test[b]	Remarks	Reference
Argentina		16 (seropositive)	100	IFAT	Dam-progeny	66
Australia		27 (seropositive)	74	ELISA (POURQUIER)	Familial	201
		27 (seronegative)	15			
Canada	Ontario	619 (seropositive)	40.7	ELISA (WT-IHCA)	Dam-daughter	334
		2,490 (seronegative)	6.7			
	Québec	144 (seropositive)	44.4	ELISA (BIOVET)	Dam-daughter	47
	Saskatoon	85 (seropositive)†	90	ELISA (VMRD)	Dam-daughter	466
		13 (seronegative)†	71			
Costa Rica		249 (seropositive)	67.5	WT-IH-ELISA	Dam-daughter	375
		498 (seronegative)	23.5			
Germany		15 (seropositive)*	94	IFAT, IB, ELISA (IDEXX)	Dam-progeny	391
		43 (seronegative)*	2			
The Netherlands		36 (seropositive)‡	88.9	ELISA (WT-IH)	Dam-calf (precolostral)	486
		14 (seronegative)‡	14.3			
		14 (seropositive)§	100			
		3 (seronegative)§	0			
		204 (seropositive)*	80	ELISA (WT-IH)	Dam-daughter	121
		248 (seronegative)*	16.5			
		190 (seropositive)†	56.8	ELISA (WT-IH)	Dam-daughter	121
		195 (seropositive)†	30.8			
		500 (seropositive)	73	ELISA (WT-IH)	Dam-daughter	125
New Zealand		115 (dam-daughter pairs)	12.5	IB	Dam-daughter	392
Spain		98 (seropositive)	50	IFAT	Dam-calf (precolostral)	344
		192 (seronegative)	7	IFAT	Dam-calf (precolostral)	344
		25 (seropositive)	48	IFAT	Dam-calf (precolostral)	344
		73 (seronegative)	0	IFAT	Dam-calf (precolostral)	344
		32 (seropositive)	90.9	ELISA (IDEXX)	Dam-progeny	281
Sweden		369 (seropositive)	85.6	ELISA (IH-ISCOM)	Dam-daughter	176
		952 (seronegative)	13.7			
United Kingdom		124 (seropositive)	95	ELISA (MASTAZYME)	Dam-calf (precolostral)	106
		248 (seronegative)	2			
United States	California	51 (seropositive)	88.2	ELISA (WT-IHCA)	Dam-calf (precolostral)	337
	California	25 (seropositive)	100	IFAT (1:80)	Dam-progeny	11
		25 (seronegative)	0			
	Nebraska	150 (seropositive)	89	ELISA (IH-ISCOM)	Dam-progeny	56
		41 (seronegative)	22			
	California	115 (seropositive)	81	ELISA (WT-IHCA)	Dam-calf (precolostral)	337
	Maryland	74 (seropositive)	43	IFAT	Dam-daughter	160

[a] Symbols: *, from herds with no evidence of point source exposure to *N. caninum*; †, from herds with evidence of point source exposure to *N. caninum*; ‡, F1 progeny of cows that had aborted previously during an outbreak; §, F2 progeny of cows that had aborted previously during an outbreak.

[b] IB, immunoblotting; WT, whole tachyzoite extract; IH, in house; WT-IHCA, kinetic ELISA (316); BIOVET, BIOVET-*Neospora caninum*, (indirect ELISA, sonicate lysate of tachyzoites; BIOVET Laboratories, Canada); IDEXX, IDEXX HerdChek *Neospora caninum* antibody (indirect ELISA, sonicate lysate of tachyzoites; IDEXX Laboratories); MASTAZYME, MASTAZYME NEOSPORA (indirect ELISA, formaldehyde-fixed whole tachyzoites; MAST GROUP, United Kingdom); VMRD, *Neospora caninum* cELISA (competitive ELISA, gp65 surface antigen of tachyzoites; VMRD); CIVTEST, CIVTEST BOVIS NEOSPORA (indirect ELISA, sonicate lysate of tachyzoites; Laboratorios Hipra S.A., Spain); IH-ISCOM, detergent-extracted tachyzoite antigen incorporated into immune-stimulating complex particles.

body synthesis. Rarely, it is possible for a seronegative dam to give birth to a seropositive calf; this may be because the cow has been infected for some time and the level of antibodies has declined to an undetectable level (85, 176, 281, 382).

Results obtained from studies with dam and progeny are summarized in Table 10. In this respect, precolostral data are noteworthy (Table 10). Up to 95% of calves were born infected. The actual congenital transmission rate was likely to be higher because, as stated above, a few positive calves are likely to be born from seronegative dams. The data from cow-calf pairs obtained after birth are not absolute, because mismatches are possible.

Anderson et al. (11) provided convincing evidence that chronic persistent infection can be passed to progeny via endogenous transplacental transmission. In their study, 25

seronegative heifers were housed with 25 seropositive heifers beginning at birth, and their progeny were evaluated for *N. caninum* infection. The seronegative heifers remained seronegative and gave birth to calves not infected with *N. caninum*. The seropositive heifers remained clinically normal but gave birth to congenitally infected calves. Seven of these congenitally infected calves were necropsied; all had histologic evidence of *N. caninum* infection, and four were recumbent (11). Presumably, cows remain infected for life and transmit *N. caninum* infection to their offspring in several consecutive pregnancies (173) or intermittently (58, 197, 486). The rate of endogenous transplacental infection may decrease in subsequent pregnancies, indicating immunity (10, 125, 375).

Although exogenous transplacental *N. caninum* infection and abortion have been induced in cows experimentally infected with tachyzoites or oocysts by several research groups using many strains (158), little is known of the distribution and persistence of *N. caninum* in tissues of postnatally infected adult cattle.

Mathematical models of *N. caninum* infections within dairy herds (175) indicate that even low levels of horizontal transmission may be important in the maintenance of the infection within herds, because transmission by endogenous transplacental infection is below 100% and thus would lead to a continuous decrease in infection prevalence in the infected herds.

Post-natal (horizontal) transmission. The ingestion of sporulated *N. caninum* oocysts from the environment is the only demonstrated natural mode of infection in cattle after birth (111, 190, 443). To date, cow-to-cow transmission of *N. caninum* has not been observed. At present there is no evidence that live *N. caninum* is present in excretions or secretions of adult asymptomatic cows. Neonatal calves may become infected after ingestion of milk contaminated with tachyzoites (110, 446), and *N. caninum*-DNA in milk, including colostrum, has been demonstrated (316, 317). However, there is no conclusive evidence that lactogenic transmission of *N. caninum* occurs in nature (120).

Venereal transmission may be possible, but unlikely, as evidenced recently in heifers experimentally infected by intrauterine inoculation of semen contaminated with tachyzoites (408), and a dose response has been observed in a titration experiment with seroconversion and maintained antibody levels in heifers inoculated with semen contaminated with 5×10^4 tachyzoites (410). Although *N. caninum* DNA has been found in the semen of naturally exposed bulls (65, 166, 327), results suggest that viable organisms, if present, are few and infrequent. Additionally, cows inseminated with frozen and thawed semen contaminated with *N. caninum* tachyzoites failed to acquire infection (70).

RISK FACTORS FOR BOVINE NEOSPOROSIS

The knowledge of risk factors for herds to acquire *N. caninum* infection and *N. caninum*-associated abortion is important for the development and implementation of measures to control bovine neosporosis. Our knowledge of risk or protective factors with respect to bovine neosporosis is based largely on retrospective cross-sectional or case-control studies. Retrospective assessment generally allows the identification of putative risk or protective factors, but conclusive data can be obtained only by prospective cohort or experimental studies. However, the repeated identification of the same risk or protective factor in several independent retrospective cross-sectional or case-control studies increases the evidence that this factor is a "true" risk or protective factor for an infection or for a disease.

The serologic prevalences of *N. caninum* summarized in Tables 4 and 5 indicate that there are considerable differences among countries, within countries, between regions, and between beef and dairy cattle (39, 112, 250, 311, 359). However, caution should be used in evaluating these results because of differences in serologic techniques, study design, and sample size used. Data reported by Bartels et al. (39) are noteworthy because the sera were tested by standardized serological techniques (460) and similar study designs. From the data it is evident that the seroprevalence of *N. caninum* is lowest in Sweden, compared with prevalences in other European countries. Results suggest that there are differences in the infection risk among different regions, within a particular region, and among different management systems. Therefore, caution should be used when transferring the results of a risk factor analysis obtained in a particular region or management system to another. One example is that in a multivariate spatial regression analysis, the factors "abundance of coyotes" and "abundance of gray foxes" are both able to explain the differences between ecological regions regarding the *N. caninum* seroprevalence in beef calves (32). The possible importance of the factor "abundance of coyotes" was corroborated when coyotes were proven to be definitive hosts of *N. caninum* (188). However, this risk factor is definitively not relevant in European countries because there are no wild living coyotes in Europe.

Epidemic and Endemic *N. caninum*-Associated Abortion

N. caninum-associated abortion in bovine herds may have an epidemic or an endemic pattern. There are reports that in the years after an epidemic abortion outbreak, the affected herd may experience endemic abortions (56, 309, 352). Abortion outbreaks have been defined as epidemic if the abortion outbreak is temporary and if 15% of the cows at risk abort within 4 weeks, 12.5% of the cows abort within 8 weeks, and 10% of the cows abort within 6 weeks (309, 399, 488). In contrast, an abortion problem is regarded as endemic if it persists in the herd for several months or years. It is likely that these two patterns of *N. caninum*-associated abortion are related to two routes by which *N. caninum* infections can cause abortion (Fig. 3) (442).

Epidemic abortions are thought to be due to a primary infection of naïve dams with *N. caninum*, probably due to ingestion of feed or water contaminated with oocysts (296, 297). Because pregnant dams may be exposed to contamination with oocysts almost at one time (point source exposure), exogenous transplacental fetal infection and the resulting abortions occur within a short period of time. The finding of low-avidity immunoglobulin G (IgG) responses, suggesting a recent infection (56, 57) in herds with epidemic abortion, supports this hypothesis (233, 296, 383, 399). Recrudescence of a

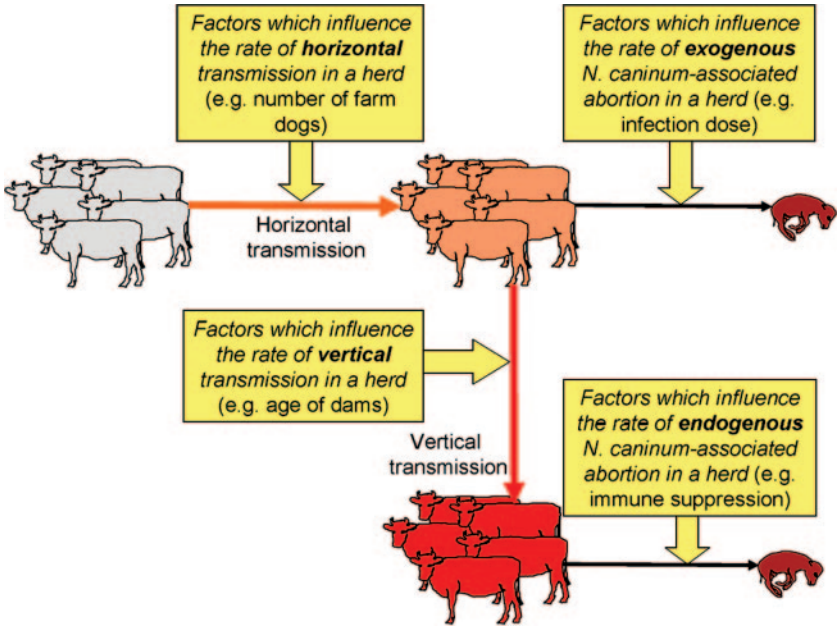

FIG. 3. Overview of potential risk or protective factors influencing the horizontal or vertical transmission of *Neospora caninum* and the occurrence of exogenous or endogenous *N. caninum*-associated abortion. In this diagram, naïve cattle are gray, postnatally infected cattle are orange, and vertically infected cattle are red.

latent infection in the dam during gestation (resulting in endogenous transplacental fetal infection) may cause abortion (197, 338, 422, 474).

Latent infection in dams may have been acquired vertically (11) or postnatally (309). The mechanism of reactivation of latent *N. caninum* infection is unknown. Whether immune suppression induced by ingestion of toxic feeds or other concurrent infections can cause reactivation has been debated but not supported by data (37, 352, 488). Recently it was shown that progesterone supplementation during midgestation increases the risk of abortion in *Neospora*-infected dairy cows with high antibody titers (46).

Irrespective of the origin of infection (exogenous or endogenous), not all congenitally infected fetuses die or become sick. In abortion epidemics, up to 57% of aborting dams have been reported (399, 488). However, in The Netherlands, high rates of seroconversion together with low-avidity responses were observed in a dairy herd, suggesting a recent exposure of this herd to *N. caninum*, though no increased abortion incidence was observed in this herd (122). If epidemic abortion is caused by an exposure to oocyst-contaminated feed or water, the observed variability regarding abortion risk may be explained by factors such as the infection dose (190), the pathogenicity of the parasite strain by which the animals became infected, and by the susceptibility of the dams (e.g., immune status, state of gestation) (190). However, nothing is known of the differences in pathogenicity of *N. caninum* isolates in cattle. Transplacental infection has been induced in cattle inoculated with *N. caninum* isolates from different sources (158).

In many cattle herds with endemic abortion due to neosporosis, there is often a positive association between the serostatus of mothers and their progeny; i.e., there is evidence that the major route of transmission in these herds is vertical (47, 54, 56, 121, 201, 391, 399, 436, 486). Several studies demonstrate that chronically infected seropositive cows can have more than a twofold-increased risk of abortion compared to seronegative dams (281, 338, 486). There are indications that the risk of endogenous abortion is influenced by the parity of the dams (284, 434). Thurmond and Hietala (434) observed a markedly increased abortion risk in congenitally infected heifers during their first gestation but not in later gestations, compared to the abortion risk in seronegative controls.

Risk Factor Studies

There are a number of risk factor studies assessing the risk of individual cattle or herds either becoming infected with *N. caninum* or experiencing *N. caninum*-associated abortions. We believe that these risks (infection risk and the abortion risk) are positively associated with each other but are influenced differently (Fig. 3). After exogenous transplacental transmission, the abortion risk might be influenced by, e.g., the number of oocysts ingested by the dam and the gestational stage (190), whereas the occurrence of abortions in endogenous transplacental transmission might be influenced by as-yet-unknown factors, e.g., the immune status of the dam.

Several studies have examined *N. caninum* infection risk at the herd level or animal level with the serostatus of herds or individual cattle (dams, calves) as dependent variables, i.e., as the target or outcome variable (Table 11). The results of these studies have been influenced by the sensitivity and specificity of the serological tests used. Fluctuations in the antibody levels of individual cattle during gestation, the gestational stage, or the gestation number could be a cause of variation (103, 173, 197, 236, 338, 360, 422). The use of seropositivity to identify infected cattle is simple but does not provide information on the

viability of infection. Furthermore, rarely, an animal may be infected but seronegative, or a seropositive animal may not have a viable infection. In addition, seropositivity also provides no information on the route of infection (horizontal or vertical) or how recently the infection occurred. To partially overcome the latter problem, some risk factor studies have focused on herds with epidemic abortion (37, 124, 488).

Infection Risk

In the following, we summarize the results of studies that have assessed risk factors for infection on either the animal or herd level.

Age of cattle. The risk of being seropositive may increase with age or gestation number in beef and dairy cattle (160, 236, 371, 386), suggesting that horizontal transmission of *N. caninum* is of particular importance in some herds. Waldner et al. (465) reported a negative age effect on the prevalence of seropositive animals in dairy cattle in Canada. In the same study it was observed that the risk of being culled was significantly greater in seropositive than in seronegative cows, suggesting that selective culling could be a possible reason for the age effect. In a recent European study it was observed that the age effect on seropositivity in dairy cattle may vary in different study areas. In Spain, for instance, the risk of being seropositive increased with age, while in Sweden the situation was the opposite (39). It was hypothesized that the age effect might be influenced by variations in the probability of horizontal transmission (e.g., by the risk of ingesting oocysts), by regional differences regarding replacement rate (influencing the time cattle may be exposed to horizontal transmission), and by management practices such as selective culling of seropositive animals (39). Nonselective culling of animals in a herd with a high seroprevalence could result in a positive relationship between age and prevalence, if the population from which successive external replacement heifers are purchased has a lower seroprevalence than the herd itself. This effect is further strengthened by the fact that the proportion of vertical transmission is often much lower than 100% (106).

A British study of cattle in dairy herds with *N. caninum*-associated problems revealed a significantly lower seroprevalence in 13- to 24-month-old animals than in cattle 7 to 12 months old and cattle older than 24 months (107). It was hypothesized that some of the 13- to 24-month-old animals (most likely heifers) were congenitally infected with *N. caninum*, although they were seronegative. Recrudescence during gestation may have caused an elevated seroprevalence in older age groups (107).

Definitive hosts (dogs and coyotes). In most epidemiological studies of dairy herds, the presence of farm dogs, either currently or within the past 10 years (339, 461), or the number of farm dogs (93, 289, 339, 402, 461) was a risk factor for seropositivity in cattle. This is not surprising, as dogs are definitive hosts of *N. caninum*. Furthermore, the putative ways by which dogs may pose an infection risk to dairy cattle have been studied (123). Defecation by farm dogs on feeding alleys and on stored grass or corn silage was reported more often by farmers of herds with evidence of postnatal bovine infection than by those of herds with no such evidence (123). Interestingly, in a study of herds with evidence of recent postnatal infection, seropositivity to *N. caninum* was more often associated with common housing than with common feeding of the seropositive age group (124). Based on these results, it may be justified to assume that contaminations of the feeding area are more closely related to infection than are contaminations of fodder during storage.

Farmers of herds with evidence of postnatal infection more often observed dogs feeding on bovine placenta, uterine discharge, and colostrum or milk than did farmers of control herds (123). This suggests that these materials may pose an infection risk to dogs; i.e., these materials may facilitate dogs becoming infected with *N. caninum*. In an experimental study, placenta, but not colostrum, has been confirmed as an infection source for dogs (120). Interestingly, feeding on aborted fetuses was not identified as a potential risk factor in herds with evidence of recent postnatal infection (123), and no oocyst shedding was observed when aborted fetuses or brains of fetuses were fed to dogs experimentally (48). However, these results were most likely influenced by the stage of autolysis in the fetus, killing the parasite along with the host cells. Most *N. caninum* organisms in aborted fetuses die with the host cells, and it is rare to find intact tachyzoites in such tissues (158). Conrad et al. (86) were able to isolate viable *N. caninum* parasites from only 2 of 49 histologically confirmed fetuses. Dogs have shed oocysts after ingesting a variety of tissues, including neural, muscular, visceral, and fetal membranes (Table 9).

There is some evidence that recently introduced dogs pose a higher risk of transmission of *N. caninum* than do resident dogs (124). This could be explained by analogy to *T. gondii*, for which it is well known that naïve definitive hosts are crucial for the life cycle (105). In *N. caninum*, the situation seems to be similar, as dogs shed no or only few oocysts after being fed repeatedly with infectious material (120, 191, 397). Additionally, higher oocyst numbers are shed by young dogs (10 to 14 weeks old) than by older dogs (2 to 3 years old) (191).

In addition to farm dogs, dogs kept in the neighborhood of farms may pose an infection risk. In a German cross-sectional study, dog densities in districts, cities, or municipalities were predictors of the prevalence of bulk-milk-positive herds (400) or were identified as risk factors for herd seropositivity (402, 461). Recently, coyotes were found to be additional definitive hosts of *N. caninum*. This was suspected after epidemiological studies of beef calves had shown that the abundance of coyotes or gray foxes in different ecological zones of Texas was associated with the seroprevalence of *N. caninum* in beef calves (32). Whether gray foxes are also definitive hosts of *N. caninum* remains to be determined. Although one experimental study indicates that the red fox is not a definitive host for *N. caninum* (398), there is an ongoing discussion as to whether red foxes or wolves could be important as sources of postnatal infections with *N. caninum*, and *N. caninum*-like oocysts in the feces of naturally infected foxes from Canada were reported (471). Recently, it was hypothesized that wolves, because of their close phylogenetic relationship to dogs, may be another potential definitive host of *N. caninum* (188). The sylvatic (deer-canid) cycle may be important in maintaining the domestic (cattle-dog) cycle of the parasite (189).

For beef cattle, there is as yet no evidence that farm dogs or dogs kept in the surroundings of farms pose an infection risk

TABLE 11. Putative risk and protective factors for *N. caninum* infections and abortions identified in epidemiological studies of dairy and beef cattle

Factor	Reference(s) identifying putative risk or sparing factor(s)[a]			
	For *N. caninum* infection		For *N. caninum*-associated abortion	
	Risk	Protective	Risk	Protective
N. caninum-specific antibodies				
Seropositivity in individual cattle	NA	NA	10, 92, 107, 109, 180, 206, 213, 236, 249, 281, 282, 289, 309, 312*, 314, 338, 393, 394, 399, 422, 436, 447, 464*, 474	
Level of *N. caninum*-specific antibodies (titer, ELISA index) in individual cattle	NA	NA	239, 285, 293, 360, 393, 394, 422, 464*, 488*	
Seroprevalence in the herd	NA	NA	37, 174, 218, 339, 382, 402, 465	
Age, parity, gestation, and lactation no.				
Age of cattle	39†, 107, 160	39†, 465*		
Mean age of cows in a herd	386*			
Proportion of heifers in a herd		386*		
Heifers, adult cattle vs calves	371†			
Gestation no.	236			
Parity			488	
Lactation no.				284, 434
Definitive hosts (dogs, coyotes) and other canids				
Dogs				
Presence of farm dogs	339, 461	33*	37	
Presence of farm dogs in the past 10 yr	461			
No. of farm dogs	93, 289, 339, 402, 461		218	
Behavior of farm dogs				
Defecation on feeding alley	123			
Defecation on grass/corn silage storage	123			
Feeding on placenta, uterine discharge, colostrum, or milk	123			
Frequency of defecation in a feed manger			218	
Density of dogs in the district or municipality of farm location	400, 402, 461			
Coyotes or foxes				
Abundance in the ecological region of the farm	32*			
Wild canids				
Frequency of observation on farm premises				218
Cats				
Presence of cats		333		
Frequency of stray cat observation				218
Other (potential) intermediate hosts				
Other animal species				
Presence of rabbits and/or dogs	333			
Presence of poultry by increasing no. of dogs	332†			
No. of poultry, >10			37	
Presence of horses			218	
Contact with sick cattle				
Calving pen used to hospitalize sick animals			37	
Grazing and fodder				
Feeding of moldy maize-silage to dairy cows during summer			37	
Feeding of remnant fodder to heifers during summer			37	
No grazing	332†			
Grazing on rangeland during summer		386*		
Use of a hay ring with round bales of hay	33*			
Use of self-contained feeders for cow supplement		33*		
Wildlife contact with the weaning ration	33*			
Source of drinking water				
Pond vs well or public water supply	333			
Colostrum or milk				
Feeding of pooled colostrum to calves	93			

Continued on following page

TABLE 11—*Continued*

Factor	Reference(s) identifying putative risk or sparing factor(s)[a]			
	For *N. caninum* infection		For *N. caninum*-associated abortion	
	Risk	Protective	Risk	Protective
Calving management				
Spring calving vs fall calving	33*			
Calving period of >3 mo		333		
Cattle density and cattle stocking density				
Stocking density	33*, 386*			
Cattle stocking density during winter	386*			
Size of farmland		93		
Herd size				
Large herds	332†			
Large herds by no. of dogs	332†			
Herd size	402			
Source of replacement heifers				
Ranch-raised replacement females	33*			
Maternal relationship			206	
Breed				
Cattle breed (e.g., native breed vs Holstein Friesian, Rubia Gallega, mixed)		39†		
Cross-breeding: using beef bull semen to inseminate dairy cattle				285
Failures during and around reproduction				
Previous abortion in congenitally infected cattle			434	
Annual rate of cows returning to estrus postpregnancy			218	
Annual rate of retained fetal membranes in herd			218	
Prevalence of retained afterbirths in previous yr, >10%			37	
Indicators for other diseases or infections				
Somatic cell count of (200–400) $\times 10^3$ vs somatic cell count of $<200 \times 10^3$		333		
Antibodies against BVDV	55		206	206
Antibodies against BHV-1	372†			
Antibodies against *Coxiella burnetii*			206	
Antibodies against *Chlamydia psittaci*				206
Antibodies against *Leptospira* sp.				206
Type of housing				
Tethered vs loose	333			
Loose housing			206	
Heifers housed on a loafing pack				218
Climate				
Mean temp in July (summer, Germany)	402			
Mean temp in spring (Italy)	371†			
Rainfall			284	
Climatic season				
Summer (The Netherlands)			488	
Winter (California)			435	
Vegetation				
NDVI	371†			
Demographic factors				
Human population	400			
Proximity to a town or village			206	

[a] *, study of beef cattle; †, study not differentiating between beef and dairy cattle (studies of dairy cattle are not marked); NA, not applicable.

(461). A possible explanation for this is that on the less intensively managed beef farms, there is in general no close contact between the excretions of farm dogs and beef cattle (33, 332, 386). Moreover, Barling et al. (33) observed that the presence of farm dogs on beef farms was a putative protective factor. That study was conducted in Texas, i.e., in the same region where it was demonstrated that the abundance of wild canids could explain the seroprevalences in beef calves. Possibly the presence of dogs was inversely related to the presence of wild canids on farm land, as suggested by Hobson et al. (218).

Other carnivores. In experimental studies, cats failed to serve as definitive hosts for *N. caninum* (295). Interestingly, there is one epidemiological study of dairy cattle that observed a protective effect for the presence of cats on a farm (333). It is possible that this factor is a confounder related to the absence of dogs. However, another possible explanation for the protective effect of the factor "presence of cats" is that cats are predators of putative intermediate hosts of *N. caninum* (e.g., mice), which could reduce the frequency by which definitive hosts of *N. caninum* have access to the tissues of infected intermediate hosts.

Intermediate hosts other than cattle. Not only cattle but also other intermediate hosts of *N. caninum* may present a source of infection for dogs and other canids. The presence of *N. caninum* DNA in naturally infected mice and rats suggests that these animals may be important sources of infection for carnivore hosts of *N. caninum* (Table 2). One study from France reported the presence of rabbits and/or ducks as a putative risk factor for seropositivity in dairy cattle (333). In a study from northern Italy, the risk of seropositivity in individual cattle increased with the number of farm dogs when poultry were present on the farm (332). Bartels et al. (37) also found the presence of poultry on the farm to be a risk factor for the occurrence of *N. caninum*-associated abortion and discussed their possible role as a vector of canine oocysts. These results warrant further examination of the susceptibility of rabbits, ducks, and other poultry to *N. caninum* and whether these potential intermediate hosts pose an infection risk to definitive hosts.

Grazing, fodder, and drinking water. Oocyst-contaminated pastures, fodder, and drinking water are regarded as potential sources for postnatal infection of cattle. Therefore, it is important to know which feeding practices pose an increased infection risk.

In the northwestern United States and Italy, grazing of cattle on rangeland during summer seems to be a protective factor (332, 386). Although wild canids and dogs have free access to rangeland, oocyst contaminations caused by definitive hosts may be too low to pose a significant infection risk or oocysts may not survive during the summer months if they are very hot and dry. Unfortunately, information on the climatic conditions under which *N. caninum* oocysts are able to survive in the environment is rare.

In beef herds, the use of a hay ring appeared to be a putative risk factor for seropositivity (33). This factor was explained by the observation that cows often calve, abort, or expel placentas near hay feeders. Because these feeders are seldom moved, it was hypothesized that fecal contaminations by definitive hosts that have fed on placentas may be concentrated close to the feeders (33). In the same study, a procedure implemented to avoid the contamination of fodder, i.e., the use of a self-contained feeder for cow supplements, was identified as a probable protective factor (33). Related to this is the observation that ranches with wildlife access to the weaning supplement had an increased risk of calves being *N. caninum* positive (33).

In a study conducted in France, the use of ponds rather than the use of a well or public water supply for drinking water was found to be a risk factor for *N. caninum* infection in dairy cattle (333). Seroprevalence data from feral marine mammals suggests that *N. caninum* oocysts may contaminate surface water and subsequently contaminate seawater (131, 154). Outbreaks of toxoplasmosis in humans have been linked epidemiologically to contaminated drinking water, and *T. gondii* has been isolated from municipal waters (60, 116).

Feeding colostrum or milk. Experimental studies have demonstrated that neonatal calves may become infected by the ingestion of milk containing tachyzoites (110, 446). However, cross-suckling of calves born to seronegative mothers on seropositive cows has not led to an infection (110). Because *N. caninum* DNA was found in bovine milk (316, 317), there is an ongoing debate regarding whether or not the lactogenic transmission of *N. caninum* is possible. With respect to this, it is interesting that one study in dairy cattle has suggested that feeding of pooled colostrum is a putative risk factor for seropositivity (93).

Calving management. In one risk factor analysis of beef calves in Texas, the effect of seasonal calving during spring was profound; i.e., the risk of calves of being seropositive was higher than it was on ranches with a fall calving season (33). No explanation for this observation was offered. Possibly, there are seasonal effects in these beef herds on the risk for calves to become infected, either by transplacental or by horizontal (postnatal) transmission. This seasonality may be biologically linked to the whelping season of the putative definitive hosts in Texas, coyotes and gray foxes. Since, naïve or young dogs are more submissive definitive hosts for *N. caninum* than are older or immune dogs (120, 191, 397), the same may also be true for young coyotes and gray foxes. Further studies are needed to explain the observations with Texas beef calves. Interestingly, in a French study, prolonged herd calving periods of 3 to 6 or 6 to 12 months reduced the risk of herd seropositivity compared to herd calving periods of up to only 3 months (333). There was no explanation for this observation.

Cattle stocking density and size of farmland. In two studies of beef calves in Texas, a high stocking density was identified as a potential risk factor for seropositivity (32, 33). A similar effect was observed for the stocking density of beef cows during winter in the northwestern United States (Idaho, Montana, Oregon, Washington, and Wyoming) (386). This effect was explained by the observation that ranches with a high density of cattle are more likely to use supplemental feeding practices (32, 33). Places on farms were supplemental feed is stored or fed to cattle may attract rodents that are potential prey for definitive hosts of *N. caninum.* This could cause these places to have an increased risk of being contaminated with the feces of definitive hosts, thus increasing the risk of postnatal infection (32).

In a study of dairy cattle in southern Brazil, it was observed that with increasing size of farmland, the seroprevalence in herds decreased. However, this protective effect was not linked to the stocking density (93). It was hypothesized that on small farms it is easier for farm dogs to have access to bovine car-

casses, aborted fetuses, placenta, and uterine discharge than on larger farms.

Herd size. In a study from Italy, the risk of individual cattle becoming seropositive increased with the size of the herd. When the analysis was restricted to data from northern Italy, the number of dogs per farm interacted significantly with herd size; i.e., the risk of being seropositive increased in larger herds with an increasing number of dogs per farm (332). In a study conducted in Germany, larger herds had an increased risk of being bulk milk positive (402). Possible explanations are that with increasing size of the herd there is an increasing chance of acquiring *N. caninum* infection by, for instance, the purchase of external replacement heifers. Another explanation for herd size as a risk factor could be that hygienic measures to prevent dogs from feeding on placentas or other infectious material are more difficult to follow with large herds than with small herds (402).

Source of replacement heifers. The vertical transmission of *N. caninum* is very efficient. Thus, the rearing of replacement heifers on the farm rather than purchasing them from outside sources supports the contention that an existing prevalence in a herd may persist for many years (176, 423). If the seroprevalence is higher in the recipient herd than in the population from which the replacement heifers were obtained, the purchase of replacement heifers should reduce infection in the recipient herd. This could explain why, in one of the risk factor studies of beef cattle, "rearing of own replacement heifers" was identified as a potential risk factor for a high seroprevalence in calves (33).

Climate. In two European studies that analyzed climate effects on the risk of seropositivity in herds or individual cattle, the factors "mean temperature in spring in a buffer zone around farm location" and "mean temperature in July in the municipality where the herd is localized" were identified as putative risk factors (371, 402). These observations can be explained by the effects of climate on sporulation or survival of oocysts. For example, a higher temperature (up to not-yet-defined limits) may favor a faster sporulation of oocysts in fodder or in the environment surrounding the cattle.

Vegetation index. An Italian study observed that the risk of seropositivity in individual cattle decreased with increasing summer normalized difference vegetation index (NDVI) values determined for 3-km buffer zones around the farm location (371). A high summer NDVI is indicative of forests or broad-leaved trees. It was assumed that cattle from the respective farms were not pastured and thus had a smaller chance of ingesting *N. caninum* oocysts. However, this interpretation is not supported by the finding of another Italian study, in which "no grazing" was identified as a risk factor for seropositivity in individual cattle (332).

Human population density. In Germany, human population density was correlated positively with dog density and could, like dog density, be used to predict the prevalence of bulk-milk-positive herds in districts and cities (400). Because dog density was identified as a putative risk factor for infection, it is not surprising that human population density seems to have the same effect.

Factors related to antibodies against other infectious agents. Björkman et al. (55) observed in Swedish cows a statistically significant association between antibodies against *N. caninum* and bovine viral diarrhea virus (BVDV). From this result it was assumed that risk factors supporting the introduction and spread of BVDV in cattle, such as high cattle density and frequent purchase of animals, also increase the risk of *N. caninum* infection. In an Italian study, a positive association between antibodies against bovine herpesvirus 1 (BHV-1) and antibodies against *N. caninum* was demonstrated (372). The possibility of whether BHV-1-induced immunosuppression after natural infection or vaccination could increase the susceptibility of cattle to secondary infection with *N. caninum* was discussed. However, to prove this hypothesis, experimental or follow-up studies after infection or vaccination are necessary (372). In a Canadian study of 78 dairy herds in Ontario, no significant association between antibodies against *N. caninum* and serostatus to *Leptospira interrogans* serovar Hardjo, Icterohaemorrhagiae, or Pomona was observed (343).

Breed. There are indications from several countries that *N. caninum* seroprevalences differ according to the cattle breed (39). However, these results must be interpreted with caution, because the differences observed might have been caused by differences in the production systems used for the different breeds and not by differences in breed-related susceptibility to infection. For example, native Spanish breeds were less likely to be seropositive than Holstein Friesian, Rubia Gallega, or mixed breeds. This was explained by differences in the intensity of management (39): in contrast to Holstein Friesian and Rubia Gallega cattle, which in Spain are more intensively managed, native breeds are predominately located on highland pastures with very low stocking densities. In the same study, breed-associated differences from Sweden were reported.

Type of housing. In a French study, tethered dairy cattle had a higher risk of being seropositive than did dairy cattle kept untethered indoors (333). No explanation for this effect was offered.

Abortion Risk

Factors having an effect on the occurrence of epidemic abortion outbreaks may completely differ from those influencing the risk of endemic abortions. Risk factor analyses often have the disadvantage that there is no information regarding the context (epidemic or endemic) in which the abortions occurred. Consequently, it is not possible to assign the risk or protective factors identified in epidemiological studies to the occurrence of epidemic or endemic abortions. Some risk factor analyses are based on case-control studies limited to herds with epidemic outbreaks (37, 488); therefore, the risk factors identified in such studies can be related only to the occurrence of epidemic abortions.

Seropositivity of individual cattle. Seropositive cows are more likely to abort than are seronegative cows, as demonstrated in a large number of studies, including retrospective and prospective cohort studies (10, 92, 107, 109, 180, 206, 213, 236, 249, 281, 282, 289, 309, 312, 315, 338, 391, 393, 394, 399, 423, 436, 447, 464, 474).

The strength of the association between seropositivity and abortion in a single group of animals may vary considerably if different serological assays are used or if for the same assay different cutoffs values are applied (392, 465). Consequently the estimates for odds ratios or relative risks may vary in relation to the serological test applied.

The abortion risk increases with increasing levels of *N. caninum*-specific antibodies in individual animals (239, 285, 293, 360, 393, 394, 423, 464, 488). De Meerschman et al. (113) found a strong association between the level of antibodies in the dam and the occurrence of histopathological lesions in aborted fetuses consistent with *N. caninum* infection. With respect to postnatal infection, a high antibody level in the individual animal could be indicative of a high infection dose and/or an efficient multiplication of the parasite in the infected host. In the case of a latent infection, a high antibody level or titer could also reflect the intensity of recrudescence of an existing infection. There is evidence from prospective studies of latently infected dams that the intensity and duration of the increase in specific antibodies during gestation could be related to the risk of fetal infection (197, 422). Thus, it might be possible to use information on individual *N. caninum*-specific antibody levels or antibody titers (and not only seropositivity) as a predictive tool for identifying animals with a high risk of abortion in herds with a high seroprevalence for *N. caninum* (360).

Seroprevalence in the herd. There are a number of case-control and cross-sectional studies that have observed that a high *N. caninum* seroprevalence in herds is associated with an increased risk of abortion at the herd level (37, 174, 218, 339, 382, 402, 488). This is explained by the increased abortion risk in latently infected as well as in recently infected individual dams (see above). However, not all herds with a high seroprevalence suffer from *N. caninum*-associated abortion (236, 339, 402). Long-term studies of herds that had experienced abortion outbreaks revealed no or only slightly elevated abortion rates in the years after the outbreak (56, 352). Recent exposure to *N. caninum* infection, as evidenced by seroconversion and low-avidity antibodies, does not necessarily result in an increased abortion rate (122). This supports the hypothesis that, in addition to infection, other factors may influence the abortion risk.

Factors related to infection risk. A number of factors putatively related to *N. caninum*-associated abortion are discussed above with respect to infection risk. Moreover, a number of factors identified as putative risk or protective factors for *N. caninum* infection in cattle also seem to influence the risk of *N. caninum*-associated abortion.

(i) Age. A case-control study of herds with epidemic *N. caninum*-associated abortion reported an increased abortion risk with increasing parity number (484, 488). However, in herds with endemic *N. caninum*-associated abortion, the association with age seems to be reversed. For example, in a study of the abortion risk in *N. caninum*-seropositive dairy cows, lactation number was identified as a putative protective factor (284). This finding confirms previous reports of a 7.4-fold-increased abortion risk in congenitally infected heifers during their first gestation but only a 1.7-fold-higher risk of abortion in the first pregnancy of the first lactation in comparison the abortion risk in seronegative controls. In the first pregnancy of the second lactation, congenitally infected cows had the same abortion risk as seronegative cows (434). In another study conducted in a herd with endemic *N. caninum*-associated abortion where endogenous transplacental infection was the main mode of transmission, Hernandez et al. (211) observed a 2.8-fold-increased abortion risk during the first pregnancy of the second lactation in seropositive dams but not in the first pregnancies of the first, third, and later lactations.

(ii) Farm dogs. The presence of farm dogs, their number, and the frequency of observation of dogs defecating in a feed manger were associated with an increased abortion risk at the herd level (37, 218). Other studies failed to identify an association between farm dogs and bovine abortion at the herd level (174, 289, 376). However, because *N. caninum*-associated abortions are not always linked to horizontal transmission but also occur in chronically infected dams, it cannot be expected that there is always a positive association between the presence or number of farm dogs and bovine abortion. One of the studies identifying a positive association between the presence of farm dogs and *N. caninum*-associated abortion had selectively analyzed risk factors for epidemic abortion. Because epidemic abortion is possibly caused by oocyst-mediated horizontal transmission, the identification of the presence of potential definitive hosts, i.e., farm dogs, as a putative risk factor is expected (37). However, at the time this study was conducted, it had not yet been established that the dog is a definitive host of *N. caninum*.

Wouda et al. (489) found a positive correlation between the seropositivity of farm dogs and increased seroprevalence in cattle, indicating a relationship between infections in dogs and in cattle. Investigated dogs were present on farms with both epidemic and endemic neosporosis (489).

(iii) Wild canids. The frequency with which wild canids were observed on farm premises seemed to have a protective effect on the likelihood that farms experienced *N. caninum*-related abortion (218). The protective effect was explained by hypothesizing a negative interaction between the presence of farm dogs (which seem to pose an infection risk) and wild canids. It was assumed that the more farm dogs are present on a farm, the lower the likelihood that wild canids are observed on the premises.

(iv) Cats. In accord with a study of infection risk (333), the frequency with which stray cats were observed on the premises was identified as a putative protective factor (218). Hobson et al. (218) assumed that the presence of cats might be an indicator of the absence of dogs, resulting in a reduced risk of horizontal transmission.

(v) Other potential intermediate hosts such as poultry and horses. Case herds having experienced *N. caninum*-associated abortion outbreaks in The Netherlands more often kept, in addition to cattle, an increased number of poultry (more than 10). As yet, there is no biological explanation for the increased risk that the presence of poultry may pose, as poultry have not yet been identified as hosts for *N. caninum* (183). However, as the infection risk seems to increase with the number of farm dogs when poultry are present on a farm (332), further examinations on the susceptibility of poultry to *N. caninum* are necessary.

Unexpectedly, a Canadian study observed an association between the number of horses on a farm and the occurrence of *N. caninum*-related abortion (218). The reason for this association is not clear. Horses are known to be intermediate hosts of *N. hughesi*, which seems to represents a species different from *N. caninum* (292). As yet, *N. hughesi* has not been isolated from cattle. Thus, it is unknown whether *N. hughesi* could be involved in bovine abortion. In addition, there is no definitive evidence that horses act as intermediate hosts for *N. caninum*.

(vi) Fodder. Feeding fodder of inferior quality, e.g., "Feeding of moldy maize-silage to dairy cows during summer" or "Feeding of remnant fodder to heifers during summer" seemed to be a risk factor for epidemic *N. caninum*-associated abortion in The Netherlands (37). The effect of feeding fodder of inferior quality may involve a suspected negative impact of fungal toxins on the immune system of cattle (37, 435, 488). In addition, remnant fodder may contain a higher proportion of contaminants, thus possibly also fecal contaminations of definitive hosts. A further explanation could be that inadequate rations may stress cattle.

(vii) Climate and season. Thurmond et al. (435) observed a highly significant seasonal pattern regarding the submission of *N. caninum*-positive aborted fetuses in California. The highest number of positive cases was submitted during winter, which in California is mild and humid in contrast to the summer, which is hot and dry. Wouda et al. (488) observed in The Netherlands that abortion epidemics most often occurred in summer, which is warm and humid. There are several possible explanations for these phenomena. Mild temperatures and humidity favor the sporulation and survival of coccidian oocysts, which may increase the risk of postnatal infection. A further explanation is that mild temperatures and humidity support the growth of fungi. Fungal toxins are suspected to cause immune suppression in cattle, which may favor the recrudescence of *N. caninum* infections in latently infected dams (37, 435, 488).

A risk factor analysis of abortion risk in *N. caninum*-seropositive dams in two Spanish dairy herds suggested that there was a significant relationship between rainfall and abortion. It was suspected that increased rainfall may pose direct and indirect stresses to cattle by elevated heat production in response to cold temperatures, behavioral stress, impaired food quality, and diminished hygiene. It was hypothesized that these stresses could trigger *N. caninum*-associated abortion in latently infected cattle (284).

(viii) Farm-raised replacement heifers. Rearing of dams affected by abortion and replacement heifers on a single farm was identified as a putative risk factor for *N. caninum*-associated abortion in a case-control study conducted in Switzerland (206). This finding is in accord with previous findings on infection risk in beef calves (33).

(ix) Proximity to a town or village. In the same Swiss case-control study, "proximity to a town or village" was observed to be a putative risk factor for *N. caninum*-associated abortion (206). This observation is in accord with the findings of a German study that showed that herds had an increased risk of being positive in an *N. caninum* bulk milk ELISA if they were located in districts or cities with a high human population density (400). An increased human population density is correlated with a high dog density (400), which may lead to an increased infection risk of herds located closer to towns or cities.

(x) Factors related to antibodies against other infectious agents. Infections with agents other than *N. caninum* could cause stress or immune suppression in animals, thus supporting the recrudescence of chronic infections or postnatal transmission (55, 431). In contrast, vaccination against other infectious agents could reduce the level of stress in a herd and thus reduce also the likelihood of *N. caninum*-associated abortions if stress triggers such abortions (218). The effect of other infections or vaccination against other infectious agents on the risk of *N. caninum*-associated abortion is not clear. Both vaccination and infection induce antibodies against infectious agents, and these serological responses can be used to address this question in epidemiological studies. However, the results of risk factor studies based on serological responses to other infectious agents are often difficult to interpret because typically there is no or only limited information regarding whether the antibodies are present because of infection or because of vaccination.

In an univariate analysis, a Swiss case-control study observed that herds with *N. caninum*-associated abortions were more often positive for antibodies against *Coxiella burnetii* and less often positive for antibodies against BVDV, *Chlamydia psittaci*, and *Leptospira* species than were control herds (206). However, in a final multivariate model, positive BVDV serology appeared to be the only putative serology risk factor for *N. caninum*-associated abortion at the herd level. The serostatus to *Coxiella*, *Chlamydia*, and *Leptospira* was eliminated from the final model because of the lack of statistical significance.

In a Dutch case-control study, no significant relationship was observed between the herd level seropositivity for BVDV, BHV-1, *Leptospira interrogans* serovar Hardjo, and *Salmonella enterica* serovar Dublin and the risk of epidemic *N. caninum*-associated abortion. However, among the aborting dams there was a negative relationship between seropositivity to BVDV and seropositivity to *N. caninum* (37).

(xi) Housing. In two studies, the type of housing had an effect on the risk of *N. caninum*-associated abortion. In a Swiss study, loose housing of cattle was identified as a putative factor increasing the abortion risk (206). Apparently, loose housing is related to unknown management practices that increase the risk of *N. caninum*-associated abortion. For example, an association between housing and herd size was identified in a German study, because in large herds cattle were more likely to be kept in pen barns (402). However, it should be mentioned that in study conducted in France, loose housing was identified as a factor that reduced the infection risk (333).

In a Canadian study, the housing of heifers on a loafing pack (a housing pen divided into feed manger, scrape alley, and bedded pack areas) reduced the abortion risk (218). It was assumed that some designs of loafing packs may hinder the access of farm dogs and that the effect is most likely associated with oocyst-mediated horizontal transmission of *N. caninum* to cattle.

Factors associated with reproduction. (i) Previous abortions. In a cohort study of the abortion risk of congenitally infected cows, it was observed that infected cows that had previously aborted had a 5.6-fold-higher abortion risk than did congenitally infected cows that had not experienced an abortion before (434).

(ii) Annual rate of cows returning to estrus postpregnancy. A Canadian case-control study revealed that there was a positive association between the occurrence of *N. caninum*-related abortions in a herd and the annual rate of cattle returning to estrus after pregnancy confirmation (218). A high rate of early pregnancy losses could increase the chance for definitive hosts to have access to infectious material, increasing the rate of oocyst-mediated horizontal transmission.

On the other hand, this result could indicate that *N. caninum*

is associated not only with abortion but also with early pregnancy losses. Indeed, there are four other studies, three from Canada, whose results support this view (319, 464, 465, 467). In this context it should be mentioned that cattle experimentally infected at day 70 postinsemination with high doses of *N. caninum* tachyzoites were more susceptible to abortion than those infected with the same dose at day 140 or 210 postinsemination (476). However, a number of other epidemiological studies observed no indication that *N. caninum* is able to cause early pregnancy losses (54, 236, 282, 283, 378).

(iii) Retained afterbirths. Two studies indicate that the risk of *N. caninum*-associated abortion may increase with in an increasing annual rate of retained afterbirths (37, 218). This factor could be associated with *N. caninum* infections in two different ways. Firstly, more retained afterbirths could provide more sources of infection for definitive hosts and thus increase the chance that oocyst-mediated horizontal transmission occurs. Secondly, *N. caninum* may not only be associated with abortion but also be involved in the pathogenesis of retained afterbirth. Further studies are necessary to clarify this point.

(iv) Use of beef bull semen to inseminate dairy cattle. In a prospective cohort study using dairy or beef bull semen to inseminate *N. caninum*-seropositive dairy cows, it was observed that the use of beef bull semen reduced the risk of abortion (285), a finding which was confirmed by another study (284). It was hypothesized that placental function might be favored in crossbreed pregnancies, possibly via an increased concentration of pregnancy-associated glycoproteins. In a recent study it was shown that *N. caninum* infection does not affect PAG-1 (pregnancy-associated glycoprotein 1) concentrations in chronically infected nonaborting cows (286). However, PAG-1 measurement seems to be a useful tool for monitoring the fetoplacental status in aborting animals (286).

(v) Use of calving pens to hospitalize sick animals. In a Dutch case-control study, it was observed that herds on farms where the calving pen is also used to hospitalize sick animals had a higher risk of having recent *N. caninum*-associated abortion epidemics than did other herds (37). The biological significance of this finding is not clear. It is very unlikely that *N. caninum* is transmitted horizontally among adult cattle, for instance via exposure to placenta or uterine effusions. As yet, all experiments aimed at infecting adult cattle or calves via oral ingestion of placental material from seropositive animals have failed (110). Therefore, it must be assumed that the factor "calving pen used to hospitalize sick animals" is linked to another as-yet-unidentified risk factor.

Attendance at cattle shows. In a Dutch case-control study, it was observed that herds that had attended cattle shows during the previous 2 years had a reduced risk of *N. caninum*-associated abortion epidemics (37). Possibly, this factor is negatively associated with the factors "rearing of own replacement heifers" (33) or "rearing the dams affected by abortion and replacement heifers on the same farm" (205) because attendance at cattle shows could indicate that a higher proportion of replacement heifers come from external sources. "Rearing of own replacement heifers" was identified as a potential risk factor for high *N. caninum* seroprevalence in beef cattle (33), and "rearing the dams affected by abortion and replacement heifers on the same farm" was identified as a putative risk factor for *N. caninum*-associated abortion in a Swiss case-control study (206).

PREVENTION AND CONTROL

Control programs at the national, regional, and farm levels are being developed in different countries to control neosporosis (87, 126, 199, 201, 328). Control programs should incorporate a cost-benefit calculation comparing the expenses of testing and control measures with the benefit of reduced economic losses due to *N. caninum* infection or abortion (41, 204, 205, 258, 369). Since, at present, neosporosis is not considered a zoonotic disease, no special measures are recommended at this stage from a public health point of view.

A general strategy to control neosporosis worldwide is not applicable because of regional differences in the epidemiology of bovine neosporosis, and it is prudent to thoroughly study regional epidemiology of neosporosis before embarking on a control program.

Economic Losses and Cost-Benefit Analyses

The major economic loss due to neosporosis is reproductive failure in cattle in many countries. In addition to the direct costs involved in fetal loss, indirect costs include professional help and expenses associated with establishing a diagnosis, rebreeding, possible loss of milk yield, and replacement costs if aborted cows are culled. The diagnosis of neosporosis-associated abortion is difficult and expensive (135, 328). Although *N. caninum*-associated abortions have been diagnosed in many countries (129, 130), there are only a few data based on examination of a large numbers of aborted fetuses. The best available figures are approximately 20% of all bovine abortions in Brazil, California, and The Netherlands (Table 12). The methods used for diagnosis are very important. The detection of *N. caninum* DNA or the detection of antibodies in the fetus cannot be relied on to establish the cause of abortion because of the high rate of asymptomatic congenital transmission of *N. caninum* in cattle. The cost of each fetal loss is variable, based on the age and genetic value of the dam and the productive capacity of the progeny.

Postnatal losses due to neosporosis are difficult to document because there are no obvious ill effects in adult cattle other than fetal loss. Culling perhaps accounts for the major loss associated with neosporosis. Cows are culled for a variety of reasons. In a retrospective study of a 2,000-cow dairy herd in California that had a history of *N. caninum*-associated abortions, *Neospora*-seropositive cows were culled 6 months earlier than were *Neospora*-negative cows. The herd had a history of *N. caninum*-associated abortions, and *N. caninum*-seropositive cows were 1.6 times more likely to be culled (432) than were cows that were seronegative. By methods identical to those used in the California study, *N. caninum* seropositivity was not associated with culling in 3,416 cows from 56 dairy herds in Ontario, Canada (98). Tiwari et al. (439) reported that in four Canadian provinces, *N. caninum*-seropositive cows were culled at a rate 1.43 times higher than were seronegative dairy cows. These differences in culling rates associated with neosporosis might be influenced by the population studied and the methods used. Bartels et al. (41) studied *N. caninum*-associated culling in 83 randomly selected Dutch dairy herds with 17 herds that

TABLE 12. Diagnosis of *N. caninum*-associated abortion in dairy cattle from selected studies based on fetal examination

Country	No. of fetuses examined	% Infected (method)[a]	Reference(s)
Argentina	188	22.8 (H), 15.4 (IHC)	311
Australia	729	21.0 (H, IHC)	58
Brazil	161	23.0 (H, IHC)	94
Germany	135	12.6 (H, IHC), 21.6 (PCR)	418
Iran	100	3 (IHC), 12 (H), 13 (PCR)	363
Korea	180	25 (H), 21.2 (H, PCR, IFAT)	244
Mexico	211	34.5 (H), 19.4 (IHC)	314
The Netherlands	2,053	17.0 (H, IHC)	483, 485
Spain	80	31.3 (H), 10.7 (IFAT, ELISA), 15.3 (PCR)	345
Switzerland	242	21.0 (PCR)	174, 382
	223	16.1 (PCR)	370a
United States	698	24.4 (H, IHC)	9, 435
	266	46.5 (H, IHC)	10

[a] H, histology.

had experienced epidemic abortions. The hazard of culling was 1.7 times more in seropositive cows than in seronegative cows from randomly selected herds; aborted cows in these herds had an additional culling rate 1.2 times higher than in normal cows. Seropositive cows from the epidemic herds were 1.9 times more likely to abort than were seronegative cows; culling data were not provided.

N. caninum may affect milk production. In one study, *Neospora*-positive cows from a 2,000-cow herd in California produced approximately 1 kg less milk than did their seronegative herd mates (433). In another study, exposure to *N. caninum* was estimated to cause a 3 to 4% decline in milk production, causing a loss of $128 per cow per lactation in a 700-cow herd in Florida (210). Romero et al. (378) reported that cows seronegative for *N. caninum* produced an additional 84.7 liters of milk in 305 days of milk production in Costa Rica. In a Canadian study of dairy cattle from the Maritime Provinces, milk production was not associated with *N. caninum* seropositivity (449). In a large case-control study of *N. caninum* seropositivity and milk production in 140 dairy herds involving 6,864 cows in Ontario, Canada, abortion status and not seropositivity affected milk production. *N. caninum*-seropositive cows produced the same amount of milk as did *N. caninum*-seronegative cows (217). The methods used in this study were the same as those employed in the California study. However, the issue is still unsettled, as a study in New Zealand reported increased milk production in *N. caninum*-seropositive cows (351). Bartels et al. (41) reported an effect on milk production in herds that had experienced an abortion epidemic. The effect was present in seropositive animals in the first 100 days in milk for only the first year after the abortion epidemic. The pathophysiological pathway of the effect of *N. caninum* infection on milk production is a mystery.

In general, less is known of the causes of abortion in beef cattle than in dairy cattle because of the difficulty of monitoring when small fetuses are expelled in the first trimester, and so there are no accurate assessments of *Neospora*-induced losses in beef cattle. While there is also no direct evidence of *N. caninum*-associated morbidity in adult cattle, a positive association between the *N. caninum* antibody status of the calf and weight gain and a projected loss of $15.62 per calf has been shown by Barling et al. (31) in a seroepidemiological study. In beef herds, the effects on culling (237, 258), weaning weight (237), average daily weight during the feedlot period (31), and reproductive performance (465) have also been estimated. The risk of being culled for any reason was 1.9 times higher for seropositive cows in eight beef herds in Canada (465). In a simulation model based on endemic *N. caninum* infection in a beef herd in Missouri, seropositivity was associated with decreased income generated by the sale of beef cattle (258).

Regional differences in cattle management systems, parasite variability and differences in study design, analytical methodology, and parameter definitions may be the cause of the variations discussed above.

Due to the distinct influences of risk factors on infection and abortion in dairy or beef cattle raised in different regions and under different management conditions, control strategies have to be different and should always be adopted on the basis of a cost-benefit analysis at the farm level that takes into account parameters such as herd type (dairy or beef) and management system, within-herd prevalence, the predominant route of transmission, existing biosecurity measures within the farm, and the calculated effects of infection on reproductive and productive performance. As an example, on farms with endogenously related abortion, efforts might be concentrated on the identification of infected animals and their culling or selective breeding. In contrast, on farms with predominantly exogenous transplacental transmission, efforts should be concentrated on reducing the chances of oral infection by oocysts shed from a putative definitive host (442). Therefore, measures to adopt in each case should depend on the estimated economic losses due to infection and abortion within each particular farm. In this sense, several studies have calculated, using deterministic and stochastic models, the production losses in beef (258) and dairy (40, 80, 204, 205, 369) cattle and the benefits obtained after evaluation of several control strategies.

There are no firm data on economic losses due to neosporosis for the cattle industry (18, 445). It has been estimated that in California approximately 40,000 abortions could be due to neosporosis, providing an estimated loss of $35 million per year (36). In Australia and New Zealand, losses are thought to be more than $100 million Australian per year (367). In Switzerland, economic losses due to neosporosis in dairy cattle were estimated to be 9.7 Euros annually (204, 205). It is of interest that in Switzerland neosporosis has been registered as a notifiable disease since 2001 (205). The total annual loss was estimated to be $2,304 for a 50-cow dairy herd in Canada (80). In The Netherlands, 76% of seropositive herds with no episodes of abortion had no economic losses, whereas in the remaining 24% of herds, the economic losses increased notably, to a maximum of 2,000 euros per year (40). Furthermore, in farms with an abortion epidemic, the costs were on average 50 euros per animal per 2 years following the abortion epidemic and excluding the losses at the time of the abortion epidemic but including premature culling, prolonged calving interval and age of first calving, milk production losses, treatment, and diagnosis (40). In beef cattle in the United States, a 5-year simulation model evaluating different control strategies concluded that in endemic *N. caninum* infected-herds, testing the entire herd and excluding the female offspring of seropositive cows as potential replacements provided the best economic return (258). In the New Zealand and Australian dairy

situation, a control strategy of "no intervention" has been reported as the optimal economic choice up to a within-herd prevalence of 18% or 21% over a 1-year or 5-year horizon, respectively. For a higher within-herd prevalence, vaccination provided the best economic result (369). In a Swiss study, the best control strategy currently available has been shown to be discontinuing breeding with offspring from seropositive cows (204, 205).

Use of Diagnostic Tools in the Control of *N. caninum*

Abortion is a major problem for livestock operations worldwide. Even in well-established and well-equipped diagnostic laboratories, the causes of more than 50% of abortions remain undiagnosed (9, 12). Establishing a cause-effect relationship between abortion and *N. caninum* is even more complex because asymptomatic congenital *N. caninum* infections are common and finding the presence of the parasite or parasite DNA does not mean that *N. caninum* caused the abortion. We have extensively reviewed the diagnosis of bovine abortions and proposed guidelines for diagnosis (135, 328). It is important to note that the figure of 20% *N. caninum*-associated abortions in cattle from California and The Netherlands (Table 12) is based on the exclusion of all other causes of abortion and the observation of *N. caninum*-associated lesions and parasites in aborted fetuses (9, 485).

Detection of antibodies in serum and in individual or bulk milk samples by techniques such as the indirect fluorescent antibody test (IFAT) and various ELISAs are optimal for the identification of infected herds (38, 57, 234, 328, 460). Serological tests can aid in the control of neosporosis in the international animal trade (310, 328), as infected animals can introduce the parasite to naïve herds or in areas where the disease does not exist or prevalence is very low. For example, *N. caninum* antibodies were not found in local breeds of cattle in Turkey (4), but imported cattle were seropositive (Table 4).

In countries with control programs under way, national or regional reference laboratories should be promoted. This idea is particularly important since the World Organization for Animal Health does not have standardized protocols for bovine neosporosis, although regional initiatives, such as COST-Action 854, "Protozoal Abortifacients in Farm Ruminants," are promoting the standardization of diagnostic measures in bovine neosporosis among official and private institutions in the European Union. Along these lines, a manual of guidelines is being prepared by several European laboratories for the diagnosis of protozoal abortifacients in farm ruminants. These guidelines will contain recommendations concerning the diagnostic procedures to be followed when dealing with neosporosis (329).

Detection of the infection and infection-abortion relationship. On farms with abortion problems, both maternal serology and abortion examinations should be carried out. In dairy herds, bulk milk testing could be used as an inexpensive tool for monitoring seroprevalence in lactating cows (38, 74, 177, 401, 453). This technique could adequately detect a 15% or higher intraherd seroprevalence in lactating cows (38). At the individual level, seropositivity in the cow denotes that an animal is infected, although the presence of antibodies does not prove that the infection caused the abortion, as many chronically infected cows are serologically positive (360); additionally, in a relatively high percentage of herds with endemic neosporosis, the infection could not be associated with economic losses (40). Therefore, antibody levels may decrease below the cutoff level after abortion (234). Once *N. caninum* infection and/or abortion in a herd has been demonstrated, estimation of the within-herd seroprevalence and investigation of the abortion pattern in the herd are highly recommended.

Investigation of the route of transmission. Intraherd seroprevalence provides information about the infection status and is to some extent related to the economic impact in the herd. However, it is the seropositivity rate in aborting cows that is essential to establishing the relationship between *N. caninum* infection and abortions (431). This rate should be significantly higher in aborting cows than in nonaborting cows. In addition, to investigate the pattern of abortion produced by *N. caninum* in the herd, it is necessary to estimate the odds ratio, which is a parameter indicative of the abortion risk for endemic or epidemic abortion. Cows and heifers were considered at risk if they had been pregnant for at least 58 to 260 days when the abortion storm started (399). An endemic pattern of abortion is often but not always related with an odds ratio of lower than 10, whereas a higher odds ratio might be indicative of an epidemic pattern (399, 431).

In the analysis of paired samples from dams and their daughters, samples from precolostral calves and the age distribution of seropositive animals contribute to determine whether the vertical or horizontal route of transmission is predominant in the herd (Table 10). If the transmission is predominantly vertical, dams and their female offspring are seropositive, as are precolostral calves, and there is a uniform distribution of seropositive animals across the age groups. In horizontal transmission of the infection, seropositive animals are in age clusters and there is a lack of association between the serological status of dams and their offspring. Age clusters of *N. caninum*-seropositive cattle may have either seronegative dams or seronegative offspring (121). Analysis of the housing and feeding history of infected groups may help to define the most probable period of postnatal infection (124). In addition, the abortion pattern and avidity values in aborting dams are essential data (56, 233, 296). To determine the avidity value of antibodies, samples obtained immediately after the abortion from a representative number (8 to 10 animals) of seropositive aborted cows should be used. In herds with an endemic pattern of abortion and high-avidity antibodies in aborting dams, the vertical route should be considered the principal route of transmission. In contrast, the presence of low-avidity antibodies with an epidemic abortion pattern must be indicative of recent exposure to *N. caninum* by the horizontal route (1, 57, 122, 399).

Testing of replacements. In addition to the identification of the main route of transmission of *N. caninum* infection in a herd, serological techniques may also help to adopt some basic measures concerning replacements. In some cases, such as with purchase or sale, a study of *N. caninum* infection in nonaborting cows is needed. It should be taken into account that in cattle antibodies may fluctuate substantially and may even drop below the cutoff value of the serological test used (85, 234, 360, 422). In some cases, sampling after a period of 4 to 6 weeks is recommended; for doubtful samples, the use of an a posteriori method such as immunoblotting is also useful (8, 39). Examination of dam-offspring paired samples could help

to define false positives and negatives in herds in which vertical transmission is predominant. Antibody detection could also be used to determine whether a newborn calf is congenitally infected (486). In such cases, a serum sample should be taken before suckling, or 6 months after birth, as colostral antibodies may cause false-positive results and maternal antibodies may persist for several months. In precolostral calves, a positive result would confirm transplacental transmission.

Control Measures

In *N. caninum*-free herds, prevention of the introduction of the infection through standard biosecurity measures is the primary goal (199), whereas in *N. caninum*-infected herds, control programs are based on decreasing the vertical transmission in a herd by reduction of the number of seropositive cattle and/or decreasing the risk of horizontal transmission of *N. caninum* principally by controlling the definitive host population as a source of oocyst contamination (87, 199, 201, 258, 368). Different control measures have been suggested, ranging from no action taken to the improvement of biosecurity on the farm, the introduction of new alternatives in the reproductive management of the herd, vaccination, and the so-called "test and cull" strategies (87, 90, 199, 201, 258, 368).

Farm biosecurity. Biosecurity is the outcome of all activities undertaken to preclude the introduction of certain disease agents into an animal population. For bovine neosporosis, the following measures are recommended to avoid the entrance of infected animals in free or infected farms and to avoid or diminish the chances of vertical and horizontal transmission in those with the presence of *N. caninum*-infected cattle.

(i) Quarantine and testing of replacement and purchased cattle. Due to the importance of vertical transmission in maintaining the infection within a herd and the potential infective role of infected bovine tissues for the definitive host, one of the most relevant tools is to purchase replacement cattle from disease-free herds or herds with records of excellent reproductive performance and to test all potential replacements. The latter measure is particularly important in *N. caninum*-free closed herds.

(ii) Prevention of transmission from dogs and other potential definitive hosts. Prevention of dogs and other potential definitive hosts from contaminating pastures and feedstuff with feces is recommended. Dog control on cattle farms has also been proposed as a mechanism for reducing infection transmission to livestock. In intensively managed dairy farms, the presence of dogs should be avoided, or at least dog-proof fencing should be provided in appropriate areas and the access of dogs to the housing zone and the barn and feed storage areas should be avoided. Appropriate hygiene regarding dog feces on pastures is also recommended. In extensively managed farms, the role of feral dogs and other putative canids as definitive hosts should be considered. On these farms, the presence of dogs could be of help to reduce the number of other wild canids (189, 379) Since young dogs shed more oocysts after infection than older dogs (191), the presence of pregnant bitches or bitches carrying litters should also be prevented in the areas mentioned above.

Dogs and other potential definitive hosts should not have access to infected tissues of intermediate hosts. The infection risk for definitive hosts can be diminished if aborted fetuses, fetal membranes, and other tissues of potentially infected cattle, which may be intermediate hosts, are disposed of safely so that dogs and other carnivores have no access to them. At least in North America, transmission between wild and domestic animals is possible, including the potential role of hunted deer in *N. caninum* transmission to hunting dogs and ultimately to domestic livestock (189). The seroprevalence of *N. caninum* antibodies in white-tailed deer in the United States is very high (Table 7). In a study from northeastern Illinois, antibodies to *N. caninum* were found in 40% of 400 deer from four sites (146), and more importantly, half of the seropositive deer had high antibody titers. The lack of association between age and seropositivity indicated transplacental transmission of infection. As of yet there is no report of *N. caninum*-associated abortion in white-tailed deer. The isolates of viable *N. caninum* from white-tailed deer were genetically similar to the isolates from cattle and dogs (457). Dogs fed infected deer tissues shed *N. caninum* oocysts (189). Thousands of white-tailed deer are hunted every year in the United States, and most of them are eviscerated in the field. Thus, deer tissues may be sources of infection in the carnivores, including dogs and coyotes, that are proven definitive hosts for *N. caninum*. These data indicate that *N. caninum* has become endemic in this host, and control of bovine neosporosis in the United States may be difficult because of the overpopulation of white-tailed deer and coyotes, which are moving toward cities. As a preventive measure in other parts of the world, it may be important to safely dispose of putative infected organs and tissues from hunted animals (deer and others) and to prevent the ingestion of these tissues by hunting dogs and wild carnivores.

(iii) Prevention of waterborne transmission. Since the source of water (pond versus well or public water supply) has been shown to be a probable risk factor for *N. caninum* in cattle (333) and waterborne transmission has been demonstrated for the closely related parasite *T. gondii* (59, 116), measures to prevent water contamination by feces from the definitive hosts should be implemented.

(iv) Rodent control. Regular rodent control by appropriate measures should be implemented to reduce the potential risk of infection that may exist in a reservoir for *N. caninum* in rodents.

(v) Prevention of putative factors for disease recrudescence in congenitally infected cattle. Giving feed of moldy fodder, which may contain mycotoxins, should be avoided. Other factors that may alter the immunity balance during gestation, such as stress and dietary imbalances, are difficult to control (37).

Reproductive management. Several reproductive management measures have been proposed to reduce the chances and the economic impact of endogenous transplacental transmission in infected herds.

(i) Embryo transfer. Transfer of embryos from infected dams into uninfected recipients can prevent endogenous transplacental transmission of *N. caninum* (25). Embryo transfer should be done only to seronegative recipient cows. *N. caninum* infection was not demonstrable in any of 70 fetuses or calves born to seronegative cows that received embryos from seropositive donors, whereas 5 of 6 calves resulting from embryo transfer from seronegative donors to seropositive recipients were infected with *N. caninum* (25). Landmann et al. (257) confirmed these findings and showed that commercially

used embryo transfer procedures also prevented transfer of *N. caninum* from seropositive cows to seronegative recipients. Additionally, preimplantation-stage bovine embryos are protected by the zona pellucida against *N. caninum* invasion (50). Thus, this technique may be used to recover uninfected calves from genetically valuable but *N. caninum*-infected dams. As a consequence, pretransfer testing of recipients for infection with *N. caninum* is highly recommended. Only uninfected cows should be used as recipients.

(ii) Artificial insemination of seropositive dams with semen from beef bulls. The results of a study conducted in Spain on two high-producing dairy farms with a mean seroprevalence of 28% suggested that the use of beef bull semen could reduce the risk of abortion in dairy cows on those farms and proposed that this effect might be due to the favorable effect of crossbreed pregnancies on placental function (285).

Testing and culling. *N. caninum*-infected cows must be considered a reservoir that may allow the parasite to spread to other cattle in the herd slowly by endogenous transplacental transmission or rapidly by horizontal spread, e.g., via ingestion of contaminated foodstuff or water. As a consequence, farmers may decide to remove infected cows or their progeny from the herd. The culling of infected cows is a control option that is effective but not always economically realistic. The "test and cull" strategy includes the following options: (i) test and cull seropositive dams or seropositive aborting dams; (ii) test and inseminate the progeny of seropositive dams with beef bull semen only; and (iii) test and exclude the progeny of seropositive dams from breeding. These options have been successfully applied, also from an economic point of view, in a few situations (201). Moreover, simulation models have estimated the economic return in endemically infected herds of beef cattle after the use of different test and cull strategies, such as culling females that fail to calve, selling seropositive females and purchasing seronegative replacements, and excluding the female offspring of seropositive dams as potential replacements. Regarding the assumptions in this model, testing of the entire herd and excluding the female offspring of seropositive dams as potential replacements provided the best economic return (258). It must be considered that these approaches can be recommended only for herds with predominantly endogenous transplacental (vertical) transmission of the infection. Culled dams or dams excluded from breeding must be replaced only by seronegative animals. Before a test and cull strategy is adopted, the risk factors for infection (main route of transmission, i.e., endogenous transplacental transmission; presence of dogs; presence of other domestic or wildlife reservoirs) must be analyzed (199). A cost-benefit analysis for each farm should be performed before any of these options is chosen. Computer programs are needed to facilitate these cost-benefit analyses.

Chemotherapy. Treatment of cattle appears to be uneconomical due to the fact that it can be used only as a preventive measure and hence must be long term, likely producing unacceptable milk or meat residues or withdrawal periods (368). However, better knowledge of host-parasite interactions during gestation may reveal strategic periods for application of short-period treatments, and different treatment strategies could be suggested for herds with predominant exogenous or endogenous transplacental transmission. Currently, there is no chemotherapy for bovine neosporosis that has been shown to be safe and effective, and any effort to treat cattle with existing drugs must therefore be discouraged at this stage. However, interesting experimental studies that may result in an option for chemotherapeutic control at a later stage have been conducted. An effect of toltrazuril and its derivative ponazuril on tachyzoites of *N. caninum* has been shown in vitro (104) and in vivo in calves (200, 255). In calves treated with ponazuril, the parasite was no longer detectable in the brain and other organs (255). In experimentally infected mice, evidence that treatment with toltrazuril may be able to block transplacental transmission of the infection was obtained (192).

Vaccination. Ideally, any vaccine developed against bovine neosporosis should protect against fetal (embryonic) loss and avoid vertical transmission. Additionally, this vaccine should allow discrimination between infected and vaccinated animals with serological tools in an integrated control approach. There is accumulating evidence that some *N. caninum*-infected cows can develop a degree of protective immunity against abortion and transmission, indicating that immunoprophylaxis is a feasible target. However, the situation seems to be different in animals or herds with predominant exogenous or endogenous transplacental transmission. In herds with endemic *N. caninum*-associated abortion, the abortion risk has been shown to be higher in heifers than in subsequent gestations in dams (211, 283), and the proportion of congenitally infected calves decreased with the increasing parity of the dams (125, 376). However, a cow can abort more than once, and infection can be transmitted to the fetus in some or all parities (10, 486). In contrast, the situation appears to be distinct in the case of exogenous transplacental transmission. On a farm with suspected point source infection, chronically infected cattle were less likely to abort than were naïve cattle (296). Moreover, naïve cattle experimentally infected prior to pregnancy did not transmit the parasite to their offspring (198, 227, 476) and induced sufficient immunity to protect against abortion when challenged on day 70 of gestation (198, 478). Vertical transmission did not occur when cows were challenged midgestation (227), showing that it is possible to induce protective immunity against exogenous transplacental transmission. This information suggests that the age at which cattle become infected is very important in determining the nature of the immune response (227, 477) and that some form of immunotolerance to parasite development in the bovine fetus exists when the infection is acquired in utero.

(i) Key points of vaccine design for bovine neosporosis. Several key points should then be considered in the design of vaccines to protect against bovine neosporosis in cattle. Firstly, *N. caninum* is an obligate intracellular parasite, and cell-mediated immunity plays a major role in protection (228). Critical components of the immune response for combating infection in cattle are gamma interferon and CD4 T cells (228, 477). The effect of antibodies in immunity remains to be determined, but a likely role would be to help control the spread of extracellular parasite stages (228). Interestingly, abortion or transmission occurs during gestation, a time when the immune response to infection can influence the success of the pregnancy, and the immunomodulation occurring in the dam to avoid rejection of the conceptus may affect the ability of the dam to control infection (228, 358). At present, it is well known that the time when infection occurs during gestation is critical to

the outcome of pregnancy (344, 360, 476). This observation has been related to the immunocompetence of the fetus at the time of *N. caninum* infection (83, 228) and to the fact that an immune response to *N. caninum* in the dam may be incompatible with survival of the fetus (228, 229, 358). Therefore, a fetus may become infected as a result of reactivation of a persistent infection in the dam (endogenous transplacental infection), following infection of the mother during pregnancy (exogenous transplacental transmission), or from a nonpregnant, naïve postnatally infected dam that gives birth to a congenitally infected offspring in a subsequent pregnancy. These are situations with fundamental differences concerning their epidemiological and control implications (442). Finally, it should be considered that different *N. caninum* strains or isolates can show notable differences in virulence, as has already been demonstrated in the mouse model (21, 84, 264, 305, 405) and observed in preliminary experimental infections of cattle (L. M. Ortega-Mora, unpublished results).

(ii) Live versus dead vaccines. The advantages and drawbacks of live and dead (or nonliving) vaccines have been reviewed extensively (228, 404, 477). Different approaches have been followed in vaccine development for bovine neosporosis, and several groups have shown that it is possible to induce at least partial protection in cattle. Andrianarivo et al. (16) reported that a POLYGEN-adjuvanted, killed *N. caninum* tachyzoite preparation failed to prevent fetal infection in pregnant cattle following intravenous or intramuscular experimental tachyzoite challenge. A HAVLOGEN-adjuvanted, killed vaccine (NeoGuard) available in a number of countries yielded protection in a field study in two out of five herds in New Zealand with an overall efficacy of 5.2% to 54% (212). The same vaccine had a "reasonable effect on abortion" when tested in Costa Rica (377), where protection was observed in 15 out of 25 herds in another field study. However, a slight negative effect was reported for six herds. The overall efficacy of the vaccine was calculated at 46%. Recently, protection against fetal death was reported for cows vaccinated with live *N. caninum* (198, 478). These results confirmed previous vaccination studies with mice, in which live infection prior to gestation protected against challenge during gestation (263, 306). However, at present, protection from endogenous transplacental transmission in controlled cattle has not been shown for any vaccine. When pregnant heifers naturally infected with *N. caninum* were immunized with killed tachyzoites or left untreated, the results suggested that reactivation of a latent infection had occurred in the naturally infected heifers, regardless of their immunization status, and that immunization with the POLYGEN-adjuvanted, killed *N. caninum* tachyzoite preparation had not been not able to prevent vertical transmission in naturally infected heifers (17).

(iii) Perspectives and recommendations. It must be emphasized that currently available vaccines do not permit discrimination of vaccinated from infected cattle with serological assays. As a consequence, after application of the vaccine, the infection status of an animal can no longer be reliably determined. All vaccinated cattle will have to be treated as infected animals, e.g., for trade purposes. Cattle vaccinated against *N. caninum* should therefore not be introduced into a *Neospora*-free herd. Seroepidemiological approaches cannot be used in vaccinated herds to determine seroprevalence in the herd regarding infection by *N. caninum*. As a consequence, diagnostic tools are restricted to analyzing aborted fetuses and to testing precolostral samples of newborn calves in vaccinated herds.

At the World Association for the Advancement of Veterinary Parasitology Conference held in Christchurch, New Zealand, in October 2005, it was agreed in the workshop "Options for Control of Protozoal Abortion in Ruminants: Practical Experience" that a document that describes the scientific information required before a vaccine against bovine neosporosis can be licensed should be prepared (87). This information should include (i) a statement on the objective of vaccination (i.e., protection against abortion, transplacental transmission, or infection in general), (ii) proof of efficacy in experimental studies performed with cattle, (iii) proof of efficacy in field studies, (iv) proof of safety, and (v) proof of compatibility with diagnostic techniques allowing testers to distinguish vaccinated from infected cattle (e.g., the addition of a marker to the vaccine or a companion test). In addition, instructions for the use of a vaccine (time, frequency of vaccination, and mode of application, etc.) must be verified by studies conducted according to scientific standards. Finally, for *N. caninum* isolates derived from bovine tissue, or from dogs that have been fed with bovine material, the absence of prions of bovine spongiform encephalopathy must be confirmed.

ACKNOWLEDGMENTS

We thank C. Bartels, E. Bártová, D. Dijkstra, S. Gennari, D. Hill, S. Nishi, A. Peregrine, M. Reichel, and W. Wouda for help in preparation of this paper.

This work was part of COST-Action 854, "Protozoal Reproduction Losses in Farm Ruminants."

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